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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

FEBRUARY 1948

PSYCHOLOGICAL ASPECTS OF OBESITY*

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A CLINICIAN of the last century divided obesity into three stages, known respectively as the enviable, the comical, and the pitiable. This is unusual language for medical classification. It illustrates well the peculiar place which obesity occupies in medicine. Obesity is not an illness, nor is it a malformation. It is here included in a program on disorders of metabolism and the endocrine glands. To a large extent this association must be considered as an expression of conformity with traditional concepts concerning the etiology of obesity. Recent studies embodying clinical as well as experimental work, bring little if any support to the view that obesity is caused by primary metabolic or endocrine disturbances; although it may happen, of course, that a person suffering from a true endocrine disorder is also obese. For those rare cases in which there is a localized organic lesion the disturbance seems to lie in central nervous regulatory mechanisms. For the great majority of fat people there is no uncontested evidence of any specific physiologic disturbance that could be regarded as the cause of obesity.

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Address before the Twentieth Graduate Fortnight, The New York Academy of Medicine, October 7, 1947.

Yet there are few conditions which cause such a distortion of the body and make a person as conspicuous as does obesity. All gradation exists and the border between the normal state of blooming good health and the abnormal state of disfiguring obesity is not at all distinct. Obesity becomes a medical problem in a strict sense only when it interferes with the well-being and efficiency of a person. Frequently it is a serious hazard to health when it is combined with other disorders such as diabetes, hypertension, orthopedic and cardiac conditions, to mention just a few. I do not wish to enumerate the many associations and interactions between obesity and other clinical disorders. Without complications obesity per se becomes a physical encumbrance only in its more extreme forms.

It has been said that there are few bodily conditions that cause quite as much unhappiness and misery as the unlovely state of corpulence. The suffering of the obese person is of a different order from that in other physical ills. It is not experienced as pain or bodily discomfort, but in a person's relationship to his fellow men. In this sense obesity belongs to the group of social and psychological disorders.

This fact that obesity becomes abnormal through its social connotations is well illustrated by the different prestige value which it carries with different people and at different historical times. With our present day attitude, for instance, it would be difficult to consider any stage of obesity as enviable. Western culture on the whole has ridiculed and despised fatness. Ancient Cretan mosaics depict women of great slimness with wasp-waists. Little wonder that the classical Greeks, their cultural successors, credited them with the knowledge of the "ideal drug"—a drug which would keep a person slim however much he ate.[1] According to an old source,[2] "Roman mothers, during the Empire, starved their daughters to make them slender as rushes and eligible in the marriage market."

On the other hand (I quote from the same source), "The Tunisians have a curious custom of fattening up their young ladies for marriage. A girl, after she is betrothed, is cooped up in a small room. The food used for this custom, worthy of barbarians, is a seed, which is of an extraordinary fattening quality; and Mr. Mungo Park tells of African mothers who cram meat down the throats of their daughters, that they may please the princes who range the great desert."

"We learn from Erasmus that the Gordii carried their admiration

so far as to advance him to the throne who was the fattest and most corpulent. And Bernier informs us that the Emperor of Mogul is annually weighed upon his birthday; when, if it appears that since his former weighing, he has made any considerable acquisition of flesh, it is matter of public rejoicings throughout his whole dominions."

These are just a few examples of extremes in evaluating obesity as a social asset or as liability, and they are partly based on hearsay tales of old travellers. Modern anthropologists have confirmed the existence of fattening houses in some African tribes, and that being fat may convey high prestige on certain people or professions. No systematic study has been made, as far as I know, of the question under what cultural conditions obesity adds to the repute of a person and under what circumstances it becomes a humiliating burden. It seems to be uncommon for obesity to be considered without special emotional significance or with indifference.

Even in our Western culture, with its general low esteem for fatness, variations in the evaluation of obesity occur as the beauty ideal changes. It is little more than a generation ago that an eminent French physician complained that "there can be no doubt that in order to have 'un décolleté impressive' each woman considers herself duty bound to be fat around the neck, the shoulders and the arms. But it is just these places where fat accumulates with the greatest difficulty. One can, therefore, be sure that the abdomen, hips, thighs and lower extremities of a woman with well padded beautiful neck and shoulders, are in a state of hopeless adiposity. . . . As to treatment, she cannot achieve a reduction of the waistline, for which she clamors, without sacrificing, in her spirit, the upper parts of the body. It is a true sacrifice to the fashionable demands. . . . Thus one finds esthetic and social factors which are active enough to make women *persist* in being obese!"

This statement sounds so alien to us and as though from a different era that one has to look twice at the title page of the book from which the paragraph was taken, to make sure that it was published in Paris in 1911.[3]

Even at the same time, and I am speaking now of contemporary observations in New York City, a wide range exists in the emotional appraisal of obesity. Opinions vary all the way from the sophisticated remarks of Ogden Nash that "Some ladies smoke too much and some ladies drink too much and some ladies pray too much, but all ladies

think that they weigh too much,"—to the undisputable dictum of the mother of a fat boy that her family thinks the bigger he is the better he is!

These remarks on the wide range of social and emotional evaluation of obesity are intended as a background for the topic of the evening. If we speak of psychological aspects of obesity it is well to remember that the remarks apply only within the cultural and social setting in which observations have been made, and only to that fraction of the large number of fat people who come for treatment.

I shall discuss the problem from three different angles, namely, (1) the psychological aspects of being obese, (2) the psychological aspects of becoming obese, and (3) the psychological aspects of treatment. This third section will also deal with the psychological attitude of the physician in regard to the diagnosis and treatment of obesity.

Psychological Aspects of Being Obese

A vivid description of the mental suffering of fatness was given by Banting in his famous "Letter on Corpulence, Addressed to the Public," published in 1863.[4] He complains: "No man laboring under obesity can be quite insensible to the sneers and remarks of the cruel and injudicious in public assemblies, public vehicles, or the ordinary street traffic; nor to the annoyance of finding no adequate space in a public assembly if he should seek amusement or need refreshment, and therefore he naturally keeps away as much as possible from places where he is likely to be made the object of the taunts and remarks of others."

Since Banting's time obesity has vastly increased in its negative rating as an object of ridicule and humiliation. This is particularly true for young obese people. They feel more or less excluded from the activities of their age group and thus fail to develop interests and social skills necessary for success and happiness in adult life. The fear of embarrassment, of making a spectacle of themselves by exposing their unshapely figure, is so great that many obese young people become withdrawn and seclusive. They give up whatever sport and physical activities they had previously enjoyed; then they avoid larger groups and finally they even stay away from friends in order not to embarrass them, as they say, by their ungainly company. The preoccupation with weight and appearance may become so grave that it overshadows all other feelings and actions. Everything is experienced in terms of

"weight" and "figure." People are classified into fat and non-fat with a feeling of contempt and hatred for the fat ones and of envy and hopeless inferiority in relation to the slender ones. Many of the personality features of obese people, their shyness and over-sensitivity, their easy discouragement in the face of difficulties or when confronted with the slightest rejection, their tendency to depressions and their phlegmatic manner may be considered sequels to their constant concern with the impression they make on account of being obese—at least it might appear so.

The practical consequences of this preoccupation with their appearance are also serious. The young fat girl who feels unattractive has little prospect of getting married, particularly if she is so convinced of being rated only according to her size that she will not even permit herself to become interested in men. For many young people the fact of being fat stands like an unsurmountable obstruction in the road toward a cherished professional goal. Again I wish to add, at least it appears so.

There are, on the other hand, many fat people who deny any difficulties in living on account of their obesity. They are cheerful and unconcerned, easy going and friendly with everybody. They seem to confirm the popular opinion that a fat man is a jovial good fellow. There may be fat people amongst us who really are content and unconcerned. They are not likely to come to medical attention, at least not for the treatment of obesity. In those happy-go-lucky fat people whom I have had the opportunity to observe, the joviality and often boisterous cheerfulness was nothing but a thin veneer put on for the benefit of the public, a compensatory defense against underlying feelings of unhappiness and futility.

The really puzzling aspect of the psychology of obese people who blame all their misery and failures in life on "being fat," is their seeming unwillingness or inability to do something about it. Ordinarily, if one recognizes the source of one's suffering, one will bend every effort to remove it. Not so the obese person. On the contrary, their very reactions to being fat contain all the elements which go toward making the condition progressively worse. If one learns to understand fat people more intimately, it gradually appears that their tremendous size, which they so loudly bemoan, is not without a positive emotional meaning for them. This is more easily recognized when dealing with obese children who say quite frankly "I would want to lose weight

but I do not want to be skinny." Usually their mothers share the anxiety about losing weight. It seems that in the insecure and unstable relations to the surroundings physical size and bulkiness convey a feeling of strength, safety and power to the timid fat child. The heavy layers of fat seem to act as protective walls against an outer world which the fat person often experiences as unfriendly and threatening. Sometimes the very unattractiveness of obesity serves a definite emotional purpose. It offers a seemingly obvious reason for avoiding situations which might provoke fear and anxiety. Many fat young girls, though outwardly very concerned about not getting married, nevertheless persist in remaining fat because it is a protection against men and sex and the responsibilities of adult womanhood which they dread even more than the disgrace of being fat.

Such an ambivalent attitude towards themselves and their condition can be recognized in many psychological reactions of obese people. The more familiar one becomes with their problems the less clear-cut are the issues. What on first impression looks like an understandable reaction to being fat reveals itself as intimately interwoven with the emotional problems of becoming obese. The withdrawal from all social contacts which fat people so readily explain as due to their obesity is usually quite out of proportion; and it often precedes or coincides with the development of obesity. I mentioned before the low prestige value of obesity in our society. This unfriendly attitude of the environment, however, is really nothing in comparison with the contempt and self-hatred that many fat people express towards themselves. There is no denying that obesity is a psychological handicap, but mainly in the sense that it becomes the focus of a derogatory attitude towards one's self which is the much more fundamental disturbance and which plays an essential role in the very development of obesity.

The Psychological Aspects of Becoming Obese

In order to understand the development of obesity, it is necessary to make a clear distinction between the mechanism of becoming fat and stimulus that sets the mechanism into operation; or, to express it differently, between the "how" and the "why."

As to the "how" there is no doubt left that obesity is the result of a positive energy balance, that means, a person becomes fat when his caloric intake is greater than his energy expenditure. In most obese

people this is brought about through a combination of over-eating and inactivity. From a caloric point of view the large food intake is usually of greater importance than the saving in energy expenditure through inactivity.

There is really nothing noteworthy about the fact that a person who persistently and grossly over-eats grows fat, particularly if at the same time physical exercise is decreased. Under normal conditions a decrease in activity is associated with a reduction of appetite. The unexplained question is *why* this normal regulation is disturbed in obesity. This question becomes answerable if we turn from physiological to psychological considerations. Eating and exercise, physiologically represented as calories in the energy balance, are at the same time very important aspects of a person's behavior. A systematic inquiry into the living habits of many obese people has revealed that these functions are endowed in the obese with an emotional meaning different from the normal. Food has an exaggerated positive value for the obese person. It stands for love, security and satisfaction. Muscular activity and social contacts, on the other hand, are associated with the concept of danger, threat and insecurity. The simultaneous occurrence of love of food and avoidance of activity becomes thus comprehensible.

Eating and activity acquire this peculiar emotional significance in a family setting which, though not specific, is characteristic for obesity. The typical obese family is of small size. Quite often it is the youngest or an only child who becomes obese. Fathers usually play a subordinate role in the emotional life of the obese family. The mothers are dominant in their influence and have a particularly close hold on the potentially obese child. Many mothers live out their own problems and frustrations in these children. They cannot give their children respect as individuals nor permit them independence and the dignity of personal achievement. These mothers try to realize in their children their own dreams of a life of luxury and idleness of which they themselves may have felt deprived. Their expression of affection is over-feeding the child and sparing him the necessary tasks of doing things for himself. The mother's attitude towards the obese child is like that toward an inanimate and prized possession, one to which they give the very best of care in order to retain it. A characteristic aspect of this possessive attitude is the frequently expressed wish for a daughter instead of a son, because these mothers feel that a daughter represents a more permanent

possession than a son. In bringing up their sons they give them the role of a daughter in their emotional life. The "feminine" characteristics of obese boys seem to be related to this attitude of the mother. There certainly is no evidence that it is an expression of gonadal dysfunction.

Mixed with the expression of affection, which over-protectiveness and over-feeding represent, is an underlying hostility which many mothers feel in relation to the fat child. Far-reaching protective measures are devised to spare the mother the anguish of her own anxiety for the safety of the child, even though these measures interfere with the child's normal psychological growth and social adjustment. At the same time the mother is irritated by the demands which this excessive care makes upon her. She nags and criticizes the child and often resorts to beating him in order to find relief from her own exasperation. Yet in her heart she wants to retain his affection and loyalty, and food is a constant bribe with which she keeps him close and dependent. As long as the child is young there is prestige for her in having a well-fed child. As the child grows older and the obesity becomes a handicap the mother is likely to be the first to nag and belittle him for his awkward appearance and to berate him for his greediness.

The family frame of obese children thus reveals influences which lead to inactivity and over-eating and distort their personality maturation. The most serious aspect in this mal-development is the interference with the development of an adequate sense of security, competence and worth-whileness. The obese child grows up with a fundamentally low self-esteem and with the conviction of his helplessness in a world which has been represented to him as a dangerous place in which he is lost without a protecting mother. Such an attitude toward life makes an individual a constant victim of uncertainty and anxiety. His only defense against this anxiety is to turn back to mother; and since the mother has been a person who was unable to give of herself but had appeased all his needs with the offering of food, food becomes his weapon against anxiety and source of comfort in periods of emotional stress. For many obese people eating is the only known source of comfort and satisfaction. Other sources of satisfaction, comfortable relations to people and the realization of inherent creative and constructive abilities, have remained seriously crippled under the unfavorable influences of his upbringing.

The first systematic inquiries into the emotional background of obesity were made on obese children.[5, 6] Numerous observations on obese adults show that there are amazingly little differences in the psychological problems between children and adults.[7, 8, 9, 10] As a matter of fact, failure to develop true emotional adulthood is an outstanding feature of obese people. This means that in the course of development the necessary emotional changes which "growing up" implies have not taken place, because every change means abandoning of old satisfaction, a step which obese people are reluctant to take. Many obese adults, like fat children, are emotionally immature, passively dependent and helpless in meeting the exigencies of life. They seek comfort in over-eating in the face of failure and of frustrating experiences.

A woman of thirty described this misuse of food in periods of emotional stress as follows: "Sometimes I think I'm not hungry at all. It is that I am just unhappy in certain things—things I cannot get. Food is the easiest thing to get that makes me feel nice and comfortable. I try to reason with myself and tell myself that these problems cannot be solved by eating." She was one of the many fat people who succeeded in showing a fairly complacent attitude towards the world during the daytime but who became tense and anxious when alone at night. As she describes it, "I think then that I am ravenously hungry and I do my utmost not to eat. My body becomes stiff in my efforts to control my hunger. If I want to have any rest at all—I've got to get up and eat. Then I go to sleep like a new-born baby."

The comparison to a "new-born baby," that is, an infantile type of reaction, is a fitting description and may well be applied to the inability of fat people to tolerate frustration or postponement of satisfaction. Though most marked in relation to food, it can be recognized in many other aspects of their behavior. Fat people are described as placid and submissive and this is often correct as far as outward behavior goes. Their fundamental attitude towards life is demanding and they do not tolerate denial of their wants. Since the genuine solution of life situations is not always available or would entail an effort on their part, food is resorted to over and over again as a substitute satisfaction.

Many of the personality features are not limited to obesity but are met with in other forms of emotional mal-development and neurosis. The specific aspect of obesity is the utilization of food for obtaining

immediate gratification or as defense against anxiety. This perverse indulgence in food is often followed by a sense of guilt and moral inferiority which in turn leads to more eating. Unless this cycle is interrupted a person will persist in being fat however much he wants to reduce his weight./I just wish to add that obese people may suffer from many other symptoms which are commonly recognized as neurotic manifestations.

Psychological Aspects of Treatment

Awareness of the underlying psychological factors leads to an understanding of the question why obesity has always presented such a baffling therapeutic problem. Viewed as a disturbance in energy balance, the treatment of obesity should be a very simple task. Reduction of the food intake and increase in exercise should and actually does accomplish a corresponding loss in weight. There is only one difficulty which makes the physiological prediction so uncertain in its clinical application. The fat patient just will not adhere to the perfect, well-balanced reducing diets which we prescribe, nor does he follow our advice for more active participation in social life that should make for his greater happiness and better adjustment.

It was this notoriously poor coöperation, particularly flagrant in the case of obese children and their parents, that prompted us at Babies Hospital to inquire into the life stories and living habits of fat people. This investigation had been at first part of a study on the endocrine factors in obesity. The observations on the growth and development of obese children which we made in the course of the investigation, stood in striking contrast to the then current assumption that hypothyroidism or hypopituitarism, or even hypogonadism were causative factors in obesity.

Looking upon the obesity problem from a historical point of view it is truly amazing that the quintessence of the cause and cure of obesity had been known since the time of antiquity. It seems that it was the application of the knowledge in the treatment of fat people which so often was found to be disappointing. The continued effort to understand this discrepancy seems to have led to many ludicrous theories about the cause, and to elaborate but useless programs of treatment of obesity. In a booklet called "Cursory Remarks on Corpulence; or Obesity Considered as a Disease: with a Critical Examination of An-

cient and Modern Opinions, Relative to Its Causes and Cure," published in London in 1816, the author, William Wadd, Surgeon,[2] summarizes the therapeutic practices of the ancient past and of his own time by saying: "The person who depends solely on the benefit to be derived from the use of any of them, will find himself grievously disappointed." He mentions as remedies the chewing of tobacco, fennel water, acids of various kinds, soap, eating of much salt to increase the absorption of fat by producing thirst, etc. Wadd proceeds to outline a plan of treatment which would be useful today even though his theories on nutrition and metabolism may sound quaint. He understood very well the reasons for the many fanciful regimes which he discards as useless: "The idea of a specific is peculiarly flattering to a patient, for whilst it encourages an implicit reliance on a single remedial process, it tends strongly to shake his confidence in the slow and disagreeable operation of diet and regimen. A gentleman who was fond of good living, and found himself becoming more corpulent than he thought convenient, having heard of the salutary effects of Mr. Wood's regimen, ordered his cook to prepare the miller's pudding, which he ate with great regularity every day after his usual dinner."

He further explains: "Many would willingly submit to any violent remedy, so that an immediate benefit could be produced; but unless the disease speedily gives way, they despair of success; consider it as unalterably connected with their constitution, and of course, return to their former habits." Wadd's remarks are as pertinent today as they were in his time. It seems that each generation has to rediscover the simple basic facts about causes and cure for obesity. Fifty years later Banting[4] in his Letter to the Public reported how he had been searching for help for many years, consulting one "high orthodox authority (never an inferior adviser)" after another and how he received many conflicting and abstruse prescriptions, all in vain, until he found the "excellent adviser" in whose honor he publishes the account of his cure which he calls "simply miraculous." Banting exclaims "Oh! that the faculty would look deeper into and make themselves better acquainted with the crying evil of obesity—that dreadful tormenting parasite on health and comfort. Their fellow men might not descend into early premature graves, as I believe many do, from what is termed apoplexy, and certainly would not during their sojourn on earth, endure so much bodily and consequently mental infirmity."

The diet which Banting outlined has been included under his name in medical textbooks. Its main features, the elimination of bread, butter, sugar, beer and potatoes are in good agreement with the diet which we would calculate today. Yet the search for more specific explanations and more specific treatment of obesity has continued, and we are just now emerging from the promise and allure of miracles to be worked by endocrine treatment.

This repetitious cycle of overlooking plain facts about obesity and of clinging to high-sounding theories may be understood if we take psychological factors into account. The correction of faulty eating habits is a central problem in treatment. Yet the importance of over-eating has been most often overlooked in the medical treatises on obesity. The occurrence of alimentary obesity, the simple or exogenous as it has been called, has never been entirely denied and it has been included in the medical classification of obesity, only to be cast aside as not quite worthy of serious scientific endeavor.

One of the reasons for this neglect of over-eating may be found in the fact that obese patients usually are very vague when asked about their eating habits. They just do not tell us how much they eat, sometimes in good faith because to them it is not "too much," more often because they are ashamed to admit it. If obesity on the whole has been looked upon in our society as a problem with little dignity, this is even more the case for the moral evaluation of over-eating or gluttony. Over-eating is looked upon as a moral weakness and self-indulgence. Even physicians may express a sarcastic attitude. I quote from the monograph of a modern writer:[11] "There is only one kind of alimentary obesity, and there are only two adjectives which can suitably be used to describe it, namely, contemptible and disgusting. Every degree of alimentary obesity is contemptible, because it denotes self-indulgence, greed and gormandizing; and most are disgusting because they represent an unsightly distortion of the human form divine, and a serious impairment of the intellectual faculties." Little wonder that this doctor, who I am sure wants to treat his patients with respect and human understanding, has to find other causes for obesity and sets out to prove that most patients are fat from "causes which are endocrine and not alimentary."

The obese patient is more than ready to accept such a so-called scientific diagnosis. It makes him the victim of some mysterious fate

and he himself does not need to exert any effort or to assume responsibility for a change in his living habits. As we have seen, the basic attitude toward life of a fat person is passive and demanding and he expects to have everything done for him. His ideal of treatment is something, anything, that will melt his fat away without effort on his part such as the "ideal drug" of the ancient Cretans, the secret of which was lost already to the old Greeks, if such a drug ever existed. It sounds too much like wish-fulfillment in the Golden Age for fat people.

Even if such a drug existed, the best it would accomplish would be a purely symptomatic treatment producing "thin fat people." By this expression I mean to say that if the fundamental attitude and life habits of fat people remain unchanged they will regain the lost weight, if not immediately, then as soon as they are faced with problems that challenge their low capacity for independent decisions and achievement.

The basis of rational treatment of obese patients is an understanding of and respectful attitude towards their genuine problems. If an obese patient, particularly the fact that he over-eats, is approached with a respectful tolerance, he is not only more frank in giving information but his efforts at reducing will be more genuine and lasting. While on a reducing diet he needs the sympathetic support of a physician who will also help him to gain insight into the nature of his real problems. This can best be accomplished by regular and continuous contact. Prescription of a diet alone is rarely sufficient. The dependent attitude of an obese patient is as much a fact of his existence as his over-eating. If we are aware of this problem we can utilize his visits to help him to achieve greater independence.

If, in order to insure regular visits to the office, some prescription is given, this will not interfere with a rational psychological approach as long as the drug is not presented as a magic pill that will do the job. There seem to be some drugs on the market which are said to have a curbing influence on the appetite and they might therefore be of direct additional help. There is, however, strong psychological objection against the use of endocrine products for treatment of so-called sexual mal-development in obese boys.[12] Cases in which there is true indication for such treatment are so exceedingly rare that they can be neglected for our discussion. In a very large number of obese preadolescent boys who are made the object of such therapeutic zeal, there is no medical justification whatsoever of exposing the family to unnec-

essary expense and the young patient to the emotional trauma of being branded as suffering from an essential physiological deficiency. Such young people are already handicapped by grave adjustment problems due to the difficulties of their background and the embarrassment of being fat. The additional psychological trauma of such unwarranted diagnosis and treatment further aggravates the situation since it seems to confirm their worst fears about being inadequate for life.

Summary

I have presented tonight a concept which treats obesity as the somatic expression of a mal-development in personality maturation. The large physical size represents symbolically the need and desire for strength and security which the fat person lacks in his human relationships. The bodily expansion may be looked upon as a vicarious expression of a thwarted personality development. The leading traits which collaborate in the production of obesity, namely, over-eating and underactivity, have in themselves a high emotional significance. They serve as a defense against anxiety and give a semblance of satisfaction which the obese person has not learned to achieve in more constructive ways.

A modern writer[13] expresses the inner awareness of a fat person that his creative potentialities are locked within him, far out of reach, by saying: "Imprisoned in every fat man, a thin one is wildly signaling to be let out." This seems to me to express the essence of the obesity problem.

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STUDIES IN INTERMEDIARY METABOLISM CONDUCTED WITH THE AID OF ISOTOPIC TRACERS*

DEWITT STETTEN, JR.

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FROM time to time, in the development of science, man has come upon a tool or technique of such obvious importance and usefulness that numerous workers in various fields have seized upon it and applied it to the solution of their problems. The discovery of logarithms in mathematical science, the perfection of the microscope in morphological science, or the development of microrespirometry and the tissue slice technique in biochemical science, may serve as examples in which, in each case, the new tool tremendously accelerated the advancement of the science, simplified the solution of many problems and made possible successful assault upon problems which had previously been unassailable. Such a tool is the currently much publicized isotope technique.

It should be stressed at the outset that the application of this technique to biochemical problems does not constitute a new science in any sense of the word. It is a new tool, and one which is very widely useful in the solution of certain types of problems. It is indeed essential for the solution of some. There are, however, many problems in the successful investigation of which isotopes are of no use whatsoever, and it must not be imagined that the isotope technique in any way supplants the classical procedures of biological investigation, synthesis, isolation, analysis, and so forth.

The use of labels in biological studies antedates by many years the use of isotopes. Perhaps the most celebrated example of this type of study stems from Knoop,[1] who labeled fatty acids by the expedient of replacing a hydrogen atom on the terminal methyl group by a phenyl. Such a molecule could readily be distinguished from other molecules of fatty acid, by virtue of its altered chemical properties, and its fate in

* Given October 10, 1947 before the Twentieth Graduate Fortnight of The New York Academy of Medicine.

the animal body could thus be followed. The very strength of this method, however, was also its weakness. Just as the chemist was able to distinguish between the labeled fatty acid and the naturally occurring unlabeled analog, so, it was feared, might the experimental animal. It might handle the labeled material by a different route or at a different rate than the naturally occurring substance and, therefore, whereas one might glean a great deal of information about the behavior of the synthetic labeled compound in the animal body, one had still to be cautious in the translation of these results to the natural analog. What was needed, clearly, was a label such that the operator could at all times detect its presence and yet so subtle that the experimental animal was unable to distinguish between labeled and unlabeled molecules. Precisely such a label has been supplied by the currently available isotopes of the biologically important elements.

If one prepares a sample of some substance which occurs naturally in the diet or in the body of an animal, operating in such a way that one or more of the constituent atoms are replaced by atoms of the same atomic number but of different atomic weight, the product which one obtains is, in general, indistinguishable by ordinary chemical means from the naturally occurring material. Not only do chemical means fail to distinguish the synthetic from the naturally occurring substance, but similarly the experimental animal is incapable of telling the one from the other. The application of suitable physical measurements, however, permits the operator not only to tell the difference between two samples, but also to determine, with high precision, the composition of any mixture of the two.

In the study of intermediary metabolism, the customary procedure is to subject the animal to some known trauma and to observe the effect of this trauma upon the metabolic processes. The withholding of some normal dietary constituent, the addition of some abnormal dietary factor, the administration of a drug or other agent, the performance of some surgical procedure upon the experimental subject, these and other insults have found usefulness in metabolic studies. A difficulty which inevitably arises in the interpretation of the results of such experiments is the matter of the extent to which the insult has rendered abnormal the metabolic process under investigation. By way of example one may cite the numerous studies of glycogenesis in which the rate of reappearance of glycogen in the liver of the previously fasted animal has been

observed. The preliminary fast, which provoked a decrease in the quantity of liver glycogen, was a necessary condition for such an experiment. Whereas the results of such a study would yield much information about the rate of glycogen synthesis in the liver of the previously fasted animal, one had to be cautious in the translation of such information to the normally nourished animal. The experimental insult was of such magnitude that it might well have influenced the very rate which was sought.

Of all the various experimental traumata at the disposal of the biochemist today, probably the one which is least traumatic is the replacement of some normal dietary constituent by the same chemical compound, some of the atoms of which are isotopic. Indeed, so slight is the trauma incident to this procedure, at least in the case of the non-radioactive isotopes, that there is no evidence whatsoever that any alteration in metabolic processes follows. Yet the study of such animals may yield a great deal of information, as will be seen from the experiments to be described, information which was essentially unobtainable prior to the development of this technique.

In discussing the problems of intermediary metabolism in which the application of the isotope technique has proven most successful, it is convenient to consider several categories in terms of the question which is raised by the investigator.

Is compound A synthesized by the tissue or the animal under investigation, or is it not?

If it is synthesized, from what precursors is it formed?

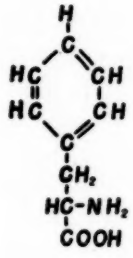
In the animal at constant weight, composition and nutrition, at what rate is tissue constituent A being destroyed and replaced by newly synthesized material ?

How are these rates affected by such variables as change of diet, disease, drug or hormone action, growth, and so forth?

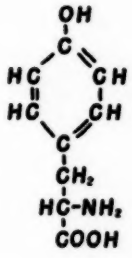
To illustrate the first category of question, I have selected as an example some work coming from Chaikoff's laboratory.[2] The question asked was quite simple: Is thyroxine synthesized in tissues other than the thyroid, or is it not? It is self-evident that if any thyroxine is synthesized in the body of the totally thyroidectomized animal, it must be very scanty, probably too little to permit of satisfactory isolation and identification by conventional chemical means. Were this not so, one would not expect to find the symptoms of hypothyroidism to follow

thyroidectomy. The workers therefore resorted to the tremendously sensitive isotope technique, taking advantage of the fact that the synthesis of thyroxine involves the uptake of iodine, and that the administration of radioactive iodine to an intact animal is promptly followed by the appearance of radioactivity in the thyroxine formed. Rats were first subjected to thyroidectomy which was subsequently proven to have been complete. Into these animals were injected minute amounts of potassium iodide containing radioactive iodine, and from the proteins of several tissue fractions, extracts were prepared which would contain thyroxine, were it present. The fact that each of these fractions was radioactive gave indication that thyroxine containing radioactive iodine had indeed been synthesized. To make the argument completely convincing, the workers now added to some of these fractions samples of ordinary, nonradioactive thyroxine, and then re-isolated thyroxine from the mixture. This procedure, the so-called carrier technique, is based upon the fact previously mentioned that isotopic and nonisotopic variants of the same molecular species are chemically identical, and consequently cannot be separated from each other by fractional crystallization. The normal thyroxine which was added would therefore become inseparably mixed with any radioactive thyroxine present in the tissue extract, and when thyroxine was re-isolated, in pure state, it would now be radioactive. This was precisely what was found to occur. The re-isolated pure thyroxine not only exhibited radioactivity, but repeated further recrystallizations, designed to separate thyroxine molecules from all other contaminating molecular species, did not produce any alteration in the quantity of radioactivity. The authors therefore necessarily concluded that atoms of iodine, administered in the form of inorganic iodide ions, were incorporated into thyroxine molecules in the tissues of their rats, this despite the fact that all vestiges of thyroid tissue had previously been extirpated. It therefore follows that the synthesis of thyroxine can and does occur in tissues other than the thyroid gland.

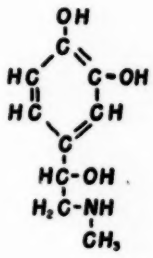
These experiments may serve to show how isotopes may be applied to the study of questions of what we have called the first category. Numerous examples might have been cited but the one selected happens to be of endocrinological interest and hence seems particularly suited to the subject matter of the present meetings. The endocrinological implications have similarly dictated my selection of an example of a



Phenylalanine



Tyrosine



Epinephrine

study falling in the second category: What is the precursor from which a compound is formed in the body?

The similarity in structure between phenylalanine, tyrosine and adrenaline has been apparent for many years, and in view of the fact that of the benzenoid amino acids only phenylalanine is required in the diet, it has been tempting to postulate that the other two compounds are made from this indispensable precursor. Until the advent of the isotope technique, however, convincing evidence bearing on this point was not at hand. The first attack upon the problem was made in Schoenheimer's laboratory[3] when phenylalanine, labeled with deuterium, was synthesized and fed to experimental animals. The tyrosine subsequently isolated from the proteins of the tissues of these animals was found to be rich in deuterium, a finding which required the conclusion that by fairly direct means, phenylalanine had been oxidized to tyrosine in the animal body.

The second attack on the problem was somewhat more subtle. The isolation of sufficient adrenaline for isotope analysis from the adrenals of a small experimental animal was entirely impractical. Gurin[4] has recently resolved this difficulty by resorting to the carrier technique mentioned previously. In a recently reported series of experiments, the preparation of two different samples of isotopic phenylalanine was described, the one labeled with radioactive hydrogen of mass 3, tritium, the other labeled with radioactive carbon C^{14}. Each of these materials was injected into rats, and after a short time the rats were killed and their adrenal glands extracted. A small amount of non-isotopic adrenaline was now added to the extract and from the mixture, adrenaline

was re-isolated. This adrenaline, after careful purification, proved in each case to be radioactive, and the authors therefore concluded that adrenaline is formed at the expense of phenylalanine. In this direct and conclusive fashion has the precursor from which the body manufactures adrenaline been identified.

The examples of successfully terminated studies in which precursors of biological compounds have been identified by the application of the isotope technique are very numerous. The foregoing example will suffice to show the type of evidence that is obtained. The suspected precursor must in general first be synthesized so as to contain one or more isotopic atoms. This material must then be administered to the experimental animal and the suspected product isolated from its tissues or excreta. The demonstration of high concentrations of isotope in the product will in general mean that it has been formed from the precursor which had been administered, and there will be very little question about the interpretation of such a result.

Problems of the third and fourth categories, those relating to rates of reactions occurring in the animal body, are often a little more complex. If one considers the normal animal at constant weight and on a uniform diet, hence presumably of constant composition in regard to body constituents, the question of the rates at which these constituents are being destroyed and simultaneously replaced by newly synthesized materials is clearly not an easy one to answer. For example, in such an animal the quantity of fatty acids in the depot fat will be constant from day to day. Yet this fat is not dead tissue, it is alive and may therefore be presumed continuously to be undergoing mobilization and destruction. The processes leading to the formation and deposition of new fat must also be proceeding, and under our conditions, must be proceeding at the same rate as the destructive processes, if the quantity is to remain constant. Starving such an animal, to deplete it of depot fat, and subsequently observing the rate of regeneration of fat on a controlled diet, will not suffice. In the first place, as mentioned earlier, the previous fast may of itself disturb the rate in question. In the second place, and perhaps more important, the rate at which fat reaccumulates in such a fasted animal is at best only the difference between the rate of deposition and the rate of mobilization.

The isotope technique offers two experimental procedures which may be employed in the evaluation of these rates. In the first procedure,

an isotopic precursor of the body ingredient under investigation is administered to the animal, and observations made, over a period of time, on the rate at which isotope accumulates in the tissue constituent. As newly synthesized molecules, each of which now will be isotopic, replace the pre-existing non-isotopic molecules of the reservoir of the substance in the body, the substance will progressively become richer and richer in isotope, approaching asymptotically some maximal value which will be determined by the quantity and isotope concentration of the precursor administered, and the reactions involved in the synthesis. Clearly the rate at which newly synthesized molecules are replacing pre-existing molecules will be related to the rate at which the isotope concentration is approaching its maximum, and in many cases, the analysis of such data permits the estimation of "turn-over" rates.

Still another procedure involves the administration, not of a precursor, but of the material itself, suitably labeled with one or another isotope. This material will, in many cases, mix with the body's store of the same compound, and in this way a labeling of the body's store will have been effected. After this preliminary operation, isotopic materials are withheld from the animal and observations made on the rate at which isotope disappears from the reservoir of compound in the animal body. In this type of experiment the newly synthesized molecules will be non-isotopic, and as they replace the pre-existing, in this case isotopic, molecules, the isotope concentration will fall, approaching zero at infinite time. Again the rate of change in isotope concentration will be mathematically related to the rate of turnover of the molecules of the tissue constituent under consideration.

Both of these procedures, if properly applied to the same body constituent, will in general give the same numerical answer for the turnover rate. The selection of procedure is often dictated by the convenience of operation or the cost of isotope required. The exact analysis of data obtained from such experiments often requires various assumptions, such as perfect mixing in the body, but the results which have been obtained have, in general, justified the assumptions which are needed.

As an example of the use of isotopes in the study of rates of turnover of body constituents in the normal animal, I should like to cite some experiments carried out by Dr. Boxer and myself[5] in which we investigated the rates of synthesis of fatty acids and of glycogen in normal rats maintained at constant weight on a uniform diet. The isotopic

precursor administered, perhaps the simplest one that there is, was deuterium oxide, heavy water, it having previously been shown that the hydrogen atoms of water contribute to the fatty acids and to the glycogen which is synthesized in the body. By the administration of heavy water we achieved a labeling of the hydrogen atoms of the body fluids. At suitable time intervals thereafter, animals were killed and samples of fatty acids and of glycogen were isolated from their tissues and these in turn were analyzed for their content of deuterium. As was anticipated, with the passage of time the concentration of deuterium in these several substances rose, and from the rate of rise in isotope concentration it was possible to calculate the fraction of each material which was synthesized each day. Since the animals were in a uniform state, it must be supposed that a similar fraction was destroyed daily. Combining this information with the quantities of materials found in the various tissues, it was possible to calculate the number of grams of glycogen and of fatty acids synthesized each day by a normal rat and it turned out that less than half a gram of glycogen and about two grams of fatty acids were thus being turned over. Comparison of these quantities with the quantity and composition of the diet consumed each day revealed that only about 3 per cent of the dietary glucose was finding its way into glycogen whereas about 30 per cent was being used each day to maintain the body's depot of fat.

Employing essentially the same technique, my colleagues and I[6] have extended this study to include the alterations of these rates that occur in certain abnormal conditions. For example, we have compared these same rates in normal rats and rabbits and in animals rendered diabetic by the administration of alloxan. This poison has been shown to exert a selective destructive action upon the beta cells of the islets of Langerhans, and hence to diminish the supply of insulin to the body. In such diabetic animals it was found that glycogen continues to be formed, but the rate of its formation from glucose of the diet was markedly reduced. More striking, quantitatively, was the decrease in the rate of fatty acid synthesis in the diabetic animals, when compared with the normal. Thus, in our rats, it turned out that the production of diabetes resulted in a fall in this rate to a value of about 5 per cent of normal. A factor which must be considered, therefore, in accounting for the loss in depot fat in uncontrolled diabetes is the failure of the animal to synthesize fatty acids at normal rate, this in addition to the well-

recognized increase in the rate of mobilization and combustion of depot fat.

It is noteworthy that the converse of this effect may be observed when insulin is injected into an otherwise normal rabbit. Again employing the same technique we have been able to demonstrate that the rate of fatty acid synthesis in the liver of an animal receiving insulin is far greater than in the liver of the normal control animal. An increase in this rate to a value of about four times normal has been observed, a finding which should be given consideration in the explanation of the gain in weight which is observed to follow insulin administration to the normal as well as to the diabetic subject.

Another type of experiment may be described to indicate how yet another variable, change in composition of the diet, may affect synthetic rates in the animal body. It has long been recognized that in the rat a severe degree of fatty liver will follow the withholding of choline from the diet. This finding has been explained on the assumption that fatty acids normally leave the liver preponderantly or exclusively in the form of the phosphatide lecithin, a large molecule for the formation of which choline is necessary. On the usual protein-poor diet, the animal's ability to make choline is markedly curtailed, and hence the liver is unable to manufacture and discharge adequate amounts of lecithin, the fatty acids synthesized in or delivered to the liver are unable to escape and fatty liver supervenes. If this is the true explanation, the quantity of choline in the diet would be expected to determine the rate of lecithin synthesis. We[7] have therefore prepared synthetic, isotopic, choline, labeled by the introduction of nitrogen of mass 15 in lieu of the normal nitrogen 14. During the first phase of the experiment, this material was added to an otherwise complete diet, and the rate of appearance of N^{15} in the choline of the lecithin of the rat's body determined. During the second phase of the experiment all choline was withheld from the diet. The isotopic nitrogen which had previously been introduced into the choline of the lecithin gradually disappeared, and the rate of its disappearance was followed. From these two rates of change of isotope concentration is was possible to calculate: Firstly, the rate at which the parts of lecithin were being assembled in the liver of the rat when choline was present in the diet; Secondly, the same rate when choline was absent from the diet, while the animal was developing a fatty liver. It was found that following the withdrawal of

choline from the diet, the rate at which lecithin was being synthesized dropped to about one third of the value which had been obtained when choline was present in the diet, this in spite of the fact that the total quantity of choline present had not changed appreciably.

Of the very many examples that might have been mentioned this evening, a few selected cases have been presented in terms as simple as possible in the hope that by so doing, an idea may be gained of the powers as well as the limitations of this method. I should like to state again, in closing, that this new tool supplements, but does not supplant, the earlier methods and conclusions of biochemistry. We have today at our disposal a label for molecules which is not only more physiological than the one that Knoop employed, but also in many cases easier to handle. Finally, I should like to record my conviction as well as my hope which is, in contrast to the impression of many popular writers on the subject, that this is not the last word in biochemical science, that the unanswered questions which will be brought to the surface by the isotope technique, or indeed by any other technique, will exceed in number the problems that it will solve.

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PENICILLIN TREATMENT OF SYPHILIS

WITH SOME REMARKS IN RETROSPECT OF SYPHILOTHERAPY OVER ONE HUNDRED YEARS*

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IT is with deep humility that the speaker participates in this Centennial Celebration of the founding of The New York Academy of Medicine. Needless to say, it is a great honor. One hundred years! What great changes have transpired in general medicine as well as in syphilotherapy and in the entire scope of this protean malady.

A long list of well-known New York names comes to mind:

Edward L. Keyes[1] showed by repeated blood examinations that mercury in small doses had a tonic effect and was the author of "The Tonic Treatment of Syphilis" (1877). Edward L. Keyes, Jr., was also a syphilographer of note.

Robert W. Taylor[2] wrote "Syphilitic Lesions of the Osseous System in Infants and Young Children" (1875) and published a large folio entitled "A Clinical Atlas of Venereal and Skin Diseases" (1889). It contained many colored illustrations of cutaneous syphilitic lesions in different stages.

L. Duncan Bulkley's[3] greatest contribution to syphilis was his "Syphilis in the Innocent" (1894) which won the Alvarenga Prize of The College of Physicians of Philadelphia (1891).

George Henry Fox[4] in 1881 published an atlas of photographic illustrations colored by hand and containing 48 plates, the first time that photography was used to depict cutaneous syphilis.

Prince A. Morrow[5] was an American pioneer in the prophylaxis

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of syphilis, a bent developed after his translation of Fournier's "Syphilis and Marriage" (1881). He founded the Society of Sanitary and Moral Prophylaxis in 1905 and served as its President. He was editor of its journal "Social Diseases" and also of "Morrow's System," a classic at the end of the century. Moreover, in this publication in 1901, W. R. Townsend,[6] an orthopedist, gave an excellent description of heredo-syphilis of the center of the face.

John A. Fordyce[7] was probably the earliest pioneer in America in the treatment of neurosyphilis and wrote the article on "Etiology of Syphilis" in Morrow's System. Bernard Sachs was also a great student of syphilis of the central nervous system.

Sigmund Pollitzer[8] was among the first American syphilologists to receive arsphenamine from Ehrlich and his "Serum Therapy and Serum Diagnosis in Syphilis" (1907) was among the earliest on the subject in our country. He was also one of the first to recommend multiple daily doses of the drug.

William B. Trimble[9] first called attention to the mottled chin in syphilis, a manifestation of early syphilis and much more common in women.

Edward B. Bronson while a dermatologist wrote extensively on syphilis and Chas. Stedman Bull,[10] an ophthalmologist of note, wrote the section on Syphilis of the Eye and its appendages in Morrow's System.

Historical: It may not be amiss to go back one hundred years and pick up a few salient items that will better show the meagre knowledge of syphilis at that time. It was generally recognized that syphilis was due to some contagious principle or miasm. Its course was partially recognized. The aftermath was not so clear.

John Hunter[11] propounded the dictum that syphilis and gonorrhea were the same disease and that only primary syphilis and gonorrhea were inoculable—that constitutional lesions and the blood were not inoculable. The work of Ricord,[12] A. Fournier[13] and Auzias-Turenne[14] in France, of Wallace[15] in Dublin, of Bell[16] and Foot[17] in England and of many others, proved conclusively that generalized lesions of syphilis were inoculable and that gonorrhea and syphilis were two different diseases.

Around 1840 to 1850 or 1860 there were several schools of thought in regard to treating syphilis. From earliest times there was one group

opposed to the use of mercury because of the terrific reactions resulting from the dosages employed. Many physicians felt that the price of health was the production of severe salivation—only then could the poison be eliminated. Chicoyneau, Chancellor of the University of Montpellier, tried to show the uselessness of salivation and rather to employ the method called extinction or elimination, i.e., restrained dosage (cited by Lancereaux,[18] p. 293). It is not, therefore, surprising that there have been published such volumes as "The Mercurial Disease" by Mathias,[19] or the one by Kussmaul[20] on "Mercurialismus" and many others. As a result Thomson, Rose, Guthrie (cited by Lancereaux[18]) and others in England treated syphilis without mercury. Many in France did likewise and in this country, Harris and Stevens (cited by Lancereaux,[18] p. 296). The Berlin syphilographer, Baerensprung (cited by Lancereaux,[18] p. 306), formally repudiated mercurial preparations and used sudorifics and Russian baths. He claimed that he had never observed tertiary syphilis in patients thus treated.

Nevertheless, by the middle of the last century, in most cases, more sober judgement prevailed. Led by such men as Ricord, Diday, Fournier, Lancereaux and Chicoyneau in France, and by Sir Jonathan Hutchinson,[21] Bell and Foote and others in England, mercury was usually the drug of choice. The protoiodide tablet was generally employed by Ricord and Fournier and hydrargyrum cum creta (gray powder) by Hutchinson. Inunctions were also employed and bichloride of mercury dissolved in various solvents and given under various names—van Swieten's drops, Dupuytren's pills, Cullerier's pills, Larrey's syrup, etc. Fumigations of cinnabar and calomel were commonly used in the first half of the last century and were still being employed at the end of the century. Moreover, vaporizations of these preparations were still recommended as late as 1901 for pustulo-crustaceous syphiloderms by White (cited by Morrow[5b]).

Girtanner used burnt sponge for venereal ulcers in the throat and Martini of Lübeck in 1826 substituted iodide with good results. In the same year Biett at the St. Louis Hospital successfully combined it with mercury. In 1831 Lugol reported cases of old syphilis cured by preparations of iodine alone (cited by Lancereaux,[18] p. 300). Wallace[22] of Dublin at the Gervis Street Hospital was the first to employ iodide of potassium, fix its dosage, point out its indications and place it almost on a level with mercury. He began his experiments in 1832 and gave the

results in lectures four years later. Ricord observed that tertiary lesions were more responsive than secondary manifestations (cited by Lancereaux[18] p. 301).

Neumann[23] tells us that Christopher Hill, Blanton and Berkeley were among the first to employ subcutaneous injections of mercury and iodine compounds in the treatment of syphilis. In 1864 Scarenzio employed calomel. It was soon found that intramuscular injections were less painful and less prone to break down. At the Charité in Berlin, Lewin in 1867 used subcutaneous injections of mercury bichloride systematically in the treatment of syphilis, but it had already been employed by Hunter in 1856 and by Hebra in 1860. Gradually other mercury compounds were introduced. Silva de Araujo of Rio de Janeiro first used salicylate. Lang introduced the use of Oleum Cinereum (Gray Oil). Edward Bronson advised injecting the base of the chancre with a mercurial salt. At least it was as rational as cauterising it as recommended by Ricord in France and by Prof. Sigmund in Vienna.

Probably one of the most unusual methods of treating syphilis was by the so-called "syphilisation" work of Auzias-Turenne.[14] He found that the person inoculated on further inoculations with the "chancrous virus," as he called it, gradually became refractory and without he or she having lost in the least good health and without showing effects of the disease. This work was taken up enthusiastically by Prof. Boeck[24] of Christiana and by Prof. Sigmund[25] of Vienna. Needless to say, it gradually fell into disrepute. In 1844 Auzias-Turenne claimed to have successfully inoculated a monkey with syphilis.

In the period when mercury and potassium iodide alone were used for treating syphilis, results in syphilis of the new-born were appalling. If the child did live, it lived a long life of recurrence after recurrence.

Arsenical Therapy of Syphilis: The discovery of the Treponema pallidum, the serologic investigations of Bordet, Gengou, Wassermann and others, the epoch making syntheses of the various Salvarsan compounds by Ehrlich[26] opened up a completely new era in the treatment of syphilis. At first the injections were given subcutaneously—the local reaction was profound and the effect on the disease far greater than anything achieved by mercury. The cure for syphilis had been found! Unfortunately, a few months later, more or less, the unfortunate patient and the physician learned otherwise. The next step was multiple injections and the elaboration by Ehrlich of further arsenical compounds.

Utopia had not yet been reached.

Bismuth Therapy of Syphilis: As far back as 1889 Balzer[27] had experimented on dogs with bismuth compounds but found them to be too toxic. Actually the dogs had died from an epidemic, presumably distemper, and not from bismuth. At any rate, he stopped further exploration on the subject. Then Robert and Sauton[28] showed the value of sodium-potassium bismuth tartrate in spirillosis of fowls. Sazerac and Levaditi[29] at the Pasteur Institute in Paris then investigated its use in syphilis. This was the beginning of another great cycle in syphilotherapy and, incidentally, the elimination of mercury.

What has happened since is too recent to deserve more than mention. Best results were achieved with early diagnosis, with continuous treatment with alternating courses of arsenicals and bismuth, with careful follow-up of the patient. With intravenous drip or even with intensive arsenical and bismuth therapy, cure could be achieved at a price. Fever therapy even entered into the picture and malaria therapy, or with the fever box, was found to be of great value in central nervous system syphilis.

It seemed that almost the ultimate had been achieved in handling this protean disease. A large proportion of the patients with acute syphilis were being cured—under ideal conditions of early diagnosis and of thorough treatment 85 to 90 per cent. Not much more could be expected when the fourth great advance came on the scene—mercury, arsenic, bismuth and Penicillin.

Penicillin Therapy of Syphilis: This new antibiotic compound was discovered by Fleming[30] and elaborated by him and H. W. Florey.[31] Its exact mode of action is not known. As Frazier[32] puts it: "Perhaps it interferes with the normal completion of some metabolic action which interferes with the growth of the cell and which leads eventually to its death." It had been found to be especially effective in streptococcal, pneumococcal, and gonococcal infections—somewhat less so in staphylococcal conditions. Again to quote Frazier: "It is the most potent, yet non-toxic antibacterial substance yet applied to the treatment of clinical disease." Once more there arose in the minds of different students, what would it do in the treatment of syphilis? At least one most competent worker in this country explored the field in rabbit syphilis and had negative findings. The penicillin being used at the time was of a crude variety and various explanations might be supplied from the standpoint

of low unitage, impurities, etc. It remained for John F. Mahoney, Arnold and co-workers[33] at the Staten Island Hospital of the United States Public Health Service to report its successful use in the treatment of four cases of early syphilis through intramuscular injections of Penicillin Sodium given every three hours, day and night, for a total of 2,400,000 units over a period of seven and one-half days.

Since then, The Penicillin Panel of The Office of Scientific Research and Development of The National Research Council, The Syphilis Study Section of the United States Public Health Service and The Rapid Treatment Centers of the United States Public Health Service through Army and Navy and U.S.P.H.S. Venereal Disease Centers, and through University clinics and hospitals, have carried on an investigation on a large scale on the value of this drug in the treatment of syphilis. Much of the credit for success thus far achieved should go to Prof. A. N. Richards and Dr. Chester Keefer of the O.S.R.D., to Dr. J. E. Moore of The Penicillin Panel, and to Dr. Udo J. Wile in charge of the Veneral Disease Rapid Treatment Centers of the United States Public Health Service. Also, much credit is due Surgeon General Thomas Parran of the U.S.P.H.S. and to Dr. J. R. Heller, Jr., Head of the Bureau of Venereal Disease of the U.S.P.H.S. for taking over the penicillin project after the close of the war.

What are results of this coöperative investigation to date? Is the work finished? Do we have tangible results? Yes, but there is still plenty to be done, wrinkles to be ironed out, dosages to be determined, methods of administration to be evaluated, etc. All agree that in some way or other a method of ambulatory treatment is a pressing demand.

When the drug was first announced and in the enthusiasm of the moment, we were almost ready to admit that now the real cure for syphilis was at hand. Remember the same thing happened with Salvarsan (606)—the clinics were besieged with syphilitics demanding the "one shot cure." Nevertheless, the situation with penicillin may be somewhat different and may promise an even better outlook than from the heavy metal therapy. At least it requires discussion under several categories.

Serologic Follow-Up of Patients: Throughout this entire discussion it is understood that the patient has already had a frank diagnosis of syphilis made clinically and either by darkfield examination or by acceptable flocculation and precipitation tests, including titration of

the reagin content of the serum. This is the base line from which the clinician must work throughout his entire follow-up of the case. One patient may be a sero-negative primary, another a sero-positive primary with 4 Kahn units, another perhaps a secondary syphilis with 64 Kahn units. This serologic titer may vary somewhat from day to day. Following treatment, the original titer perhaps of 8 Kahn units may rise to 32 in a period of a few weeks and then over a matter of several months perhaps drop to complete negativity. Again, the titer one month may be 8 units and perhaps the next 16 units—this means little of itself. It is the over all trend of the titration curve that counts—especially in early treated syphilis, in syphilis and pregnancy and in suspected or treated early congenital syphilis. A patient with early treated syphilis is not considered cured until his serologic titer has been completely negative for one year after completion of treatment. Also, he or she must have a normal physical examination, lumbar puncture and complete cardio-vascular studies. A persistent titer of 8 Kahn units over a period of 12 months in early syphilis would indicate sero-persistence and demand re-treatment. A persistently rising titer indicates trouble in a suspected primary or in a suspected congenital syphilis. In such cases a titered specimen may be necessary every week or so. We reiterate, all penicillin treated cases of early syphilis require a monthly titered serologic check-up, as well as physical examination.

Reactions from Penicillin Treatment: One of the great advantages of penicillin over heavy metal therapy lies in the absence of reactions[34] —severe in type. While the Herxheimer reaction is seen earlier and is more intense than after heavy metals this is, if anything, favorable in an early syphilis. In a syphilis and pregnancy, or in a central nervous system syphilis or in a syphilitic nephrosis, it might indicate lowered dosage for the first two days. A generalized erythema is not uncommon and occasional cases of erythema multiforme and even of erythema nodosum have been seen. These are rare and dermatitis exfoliativa is exceedingly rare. We know of but one such fatal case reported by Barksdale.[35] Urticaria is occasionally encountered, especially after Penicillin Calcium P.O.B., and may not show up for several weeks and be quite troublesome. In rare instances the localized type with angioneurotic edema may ensue—this might be a serious complication and must be kept in mind. Fortunately, thus far, no severe involvement of the hematopoietic system has been reported. Barksdale has also seen some

cases of neuritis following penicillin therapy and we have also encountered one. In some instances "id" reactions on the skin have been seen in individuals suffering from dermatophytosis.

Routes of Penicillin Administration: The drug should not be employed orally or rectally in the treatment of syphilis–at least in the present state of knowledge. The dosage is inexact, absorption is problematical and cost prohibitive. While penicillin may be administered by intravenous drip, the difficulties of administration, of thrombophlebitis and of immobilization of the patient are too great. Intrathecal administration is also unwise because of reactions in the meninges, even leading to adhesive spinal arachnoiditis and transverse myelitis.[36]

The desire in penicillin therapy is to achieve and hold a continuous high blood level of the drug. This may easily be obtained by intramuscular injections every two to three hours, provided sufficient dosage is employed.

Treatment of Early Syphilis with Penicillin Sodium in Saline or Distilled Water: Results of this form of therapy have been found to be successful in a large number of cases. In fact, they have been so successful that we are now seeing the phenomenon of reinfection on a far higher scale than heretofore. Some men would even put it as high as 20 to 30 per cent. This may be somewhat exaggerated, but it is actually frequently occurring. To attain this cure, it is necessary that the diagnosis be made as early as possible, that a sufficient dosage be employed and that the patient be followed with a serologic titered check-up every month until the reaction has been completely negative for one year. True, there has been a period recently where there was a change in the fractions of penicillin and the use of too much K[37] fraction which is rapidly destroyed in the body. This has now been changed and penicillin is made of G, F and X fractions. Crystalline G is now being used exclusively. Because of this and of the relapses occurring while so much K fraction was used, it is recommended that in sero-negative primary syphilis a dosage of not less than 3,600,000 units be employed (ninety injections of 40,000 units each every two hours, or sixty injections of 60,000 units each every three hours). For a seropositive primary or early secondary syphilis, this dosage should be increased to not less than 5,400,000 units (ninety injections of 60,000 units each every two hours or of sixty injections of 90,000 units each every three hours). With a late secondary syphilis, it would be well to

increase this dose to a total of 7,200,000 units over a period of 7½ days. *In all cases, careful monthly serologic titered check-ups are necessary.*

Treatment of Early Syphilis with Penicillin Combined with Arsenoxide and Bismuth: Many investigators lost confidence in penicillin as a result of the large number of relapses[37] encountered from the use of low dosage penicillin and from the results during the period in the last half of 1945 and early 1946 when penicillin sodium with an increased K fraction was being used. Moreover, Thomas[37] and others had already shown that penicillin therapy combined with arsenoxide had half the treatment failures seen with penicillin alone. Schoch[38] had also shown a somewhat similar situation with additive bismuth therapy. Thomas added 40 mgs. of arsenoxide daily to the penicillin schedule of 7½ days. O'Leary[39] has suggested four daily doses of arsenoxide, each 40 mgs., then the penicillin sodium was started on the 5th day, 40,000 units every three hours for a total of 2,400,000 units. On the last day of the penicillin schedule, a course of bismuth subsalicylate injections was started, 1 cc. of a 10 per cent suspension every five days. Heller[40] has recently reported the results of combined schedules of penicillin, arsenoxide and bismuth as used in the Rapid Treatment Centers under the direction of Wile. The combination of 1,200,000 units of Penicillin Sodium plus five injections of arsenoxide and three of bismuth subsalicylate over a period of ten days was satisfactory. The joint statement[41] of the Committee on Medical Research, the United States Public Health Service and the Food and Drug Administration, suggests an additive dose of arsenoxide, 300 to 360 mgs., administered in divided intravenous injections of 40 to 60 mgs. each, over a total period of one to four weeks. It is emphasized by them, correctly, that there is an added risk if this arsenic be given over a period of seven to nine days and much less if it is drawn out over four weeks.

Late Latent Syphilis and Late Cutaneous and Osseous Syphilis: It is our feeling that in all late syphilis the patient deserves a preliminary course of heavy metal (bismuth) plus potassium iodide to obviate the danger of a Herxheimer reaction or of a therapeutic paradox with too rapid healing of perhaps vital structures and resultant scar formation and contractures. Following this, the course of penicillin, 3,600,000 to 5,400,000 units, may be administered. In late latent syphilis, the physician should not commit the error of treating a persistently positive serologic reaction.

Syphilis and Pregnancy: At the recent meeting of the American Academy of Dermatology and Syphilology in Cleveland, Ingraham[42] reported that in 125 cases of syphilis in pregnancy there had been ninety-seven per cent success with penicillin. His two failures were in cases treated with 1,200,000 units of penicillin. He reported that investigations have shown the penicillin to penetrate the placenta from the tenth week on. His results have been amply confirmed by everyone who has investigated this field of syphilis. Ingraham thinks penicillin has no abortifacient effect or tendency to bring on a miscarriage. However, I think that in all pregnant women with frank secondary syphilis it is well to cut down the dosage of penicillin for the first two days to one-half, and then raise it to full dosage. For example, with a dosage of 40,000 or 60,000 units every two or three hours, it would be well to cut it down to 20,000 or 30,000 units for the first two days. All writers recommend that diagnosis and treatment be given as early as possible though even in the last month of pregnancy with a viable child it is possible to institute treatment and have a child born alive, but still showing its mother reagin. This will usually disappear by the third month. All such children should have monthly titered serologic tests. If the titer does not drop to normal or if there be a tendency for the curve to rise, treatment should be instituted. A child with titer remaining negative and with negative physical and radiologic examination for one year may be considered free from the disease.

Treatment of the Syphilitic Child: In the syphilitic babe, one must consider not only the syphilis but also the infant's general condition. It may well be that supportive measures will be as much in order as specific medication. Perhaps a few intramuscular injections of aqueous sodium bismuth tartrate, Searle, 1 cc., will lessen the Herxheimer effect in a feeble child. The Syphilis Study Section would recommend for infants a total dosage of 100,000 to 400,000 units per kilogram (2.2 lbs.). In older children the dosage may be on a unit for weight basis—with minimum dose of 60,000 units per kilogram corresponding to the minimum total of 3,600,000 units for the adult. The results are good, but not as good as in syphilis in pregnancy. Penicillin seems to be of little value for interstitial keratitis of late congenital syphilis—malaria therapy is preferable and, is, in fact, almost a specific.

Syphilis of the Central Nervous System: Outside of syphilitic meningitis, the value of penicillin is still debatable. While it has an adjuvant

value and furnishes a sense of well being, it is a problem requiring still more data before anything too definite can be offered. Penicillin added to malaria probably enhances the value of the fever treatment. True, opinions differ.

Penicillin Calcium in Peanut Oil and Beeswax—Ambulatory Treatment: What is needed above everything else is ambulatory treatment for syphilis. Cost of hospitalization would be obviated, the patient would lose no work and, too, that sense of secrecy so necessary in this disease would be assured. While it is too early to make a clear cut statement, the reports of Romansky et al.[43-46] seem very promising after use of single daily intramuscular injections of calcium penicillin, 300,000 units, in peanut oil and 4.8 per cent beeswax (by weight), hereafter spoken of as P.O.B. There seems to be no danger of foreign body tumors and blood levels of penicillin after the above dosage remain at a therapeutic level for twenty-four hours in a large proportion of the cases and with its cumulation after successive doses should be even higher. Probably the patient should receive at least sixteen daily doses or, better yet, twelve daily doses of 600,000 units and, until the problem is clearer, adjuvant arsenical and bismuth therapy—perhaps ten arsenicals administered three injections the first week and twice a week thereafter and bismuth injections, twelve in number, to follow the penicillin.

A warning should be issued as to the use of this form of therapy. The injections must be given daily, not every other day, not every week or when the patient feels like it. It is not like giving an injection of a bismuth salt. The whole theory of its use is based on the injection of a daily dosage—otherwise, blood levels fall and a penicillin-fast organism may be developed and certainly relapse will occur and perhaps infection of others as all physicians treating syphilis have observed.

One of the real objections to the use of this compound is the careless manner in which physicians use it for the one day treatment of Gonorrhea. He is not observant enough of the case to look for possible beginning genital lesions nor does he follow his patient up with a monthly serologic check-up for at least four months to rule out a hidden syphilis contracted at the time of the gonorrheal infection, but as yet not diagnosticable. All of us have seen far too many of these cases—with resultant infection of wives and sweethearts and relapse syphilis in the patient.

As in all other forms of penicillin therapy, titered serologic reactions

on these patients are a "sine qua non" until the monthly reactions have been completely negative for a period of one year. The great danger with this technique is that the patient and the doctor are liable to take the thing too lightly and neither one to realize his responsibility. Too often no titered serologic studies are made and the patient is not followed up.

From a few observations we have been able to make, irregular use of penicillin P.O.B. may lead to the production of a penicillin resistant organism which can only be treated with heavy metals.

Conclusions

And so our view of penicillin treatment of syphilis, along with some observations of syphilotherapy of the past century comes to an end.

Of the drugs, Mercury, Potassium Iodide, arsenicals, bismuth and penicillin, mercury, at least, is relegated to history.

I am not sure but that in late syphilis the physician is making a mistake in forgetting potassium iodide at the onset of therapy.

Whether bismuth and arsenicals will also be eventually dropped, only time can tell. For the present at least, they are still of great value in cases relapsing to penicillin and bismuth especially for preliminary treatment of old syphilis to be handled by penicillin.

It is to be wondered what the next century will teach us in handling this old scourge of mankind. Perhaps some perfection of penicillin or of some other antibiotic worked out by a Fleming or Florey or Mahoney may close the book for good. At least this will be the desire of every medical man.

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SURGICAL MANAGEMENT OF DIABETES: INCLUDING AMPUTATIONS*

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THE surgical aspects of the management of diabetes divides itself into the diabetic who requires a surgical operation such as, the removal of a diseased gall bladder or appendix and the treatment of surgical conditions to which the diabetic is particularly subject, such as carbuncles or gangrene.

Life expectancy has increased from forty to sixty years in the last century with better medical and surgical conrol of epidemic and degenerative diseases and if like advances continue, twice as many people over sixty-five will be alive by 1990 as today. A much larger group of patients is arriving thus at the age when surgical procedures are to be expected. This is particularly true of the diabetic. Joslin this year estimates that there are one million diabetics in the U. S. A. There are ten times more admissions for diabetes to large hospitals today than in 1910. A figure of 2.8 per 1,000 admissions in 1910 at Bellevue is contrasted with 2.1 per 100 of all admissions at the Post-Graduate Hospital averaged for the last five years (Tables I and II). While before most diabetics died early of their disease or its complications, with increasingly improved medical management of diabetes and thus greater longevity more patients will reach this surgical age. A thorough understanding of their surgical management is important because one out of every two diabetics requires a surgical operation sometime before he dies.

In reviewing the literature on the diabetic who required surgery one is impressed with the great change that has occurred with diabetic control inaugurated with insulin. Surgery for the diabetic became safe that day twenty-five years ago. It has not been sufficiently impressed on many physicians, however, and at times procrastination and even ineffective therapeutic measures are utilized in place of necessary opera-

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TABLE I—NEW YORK POST-GRADUATE HOSPITAL

Clinic Attendance—Yearly (average of 5 years)

Total Clinic Attendance		124,308
Total Diabetic Clinic	1815	3700
Total Diabetics in Vascular Clinic	1885	

.2% of all Clinic Attendance Have Diabetes

TABLE II—NEW YORK POST-GRADUATE HOSPITAL

Vascular Surgery Service

Diabetes Mellitus

5 Year Total Hospital Admissions...	53,267	Average per year...	10,653
5 Year Total Diabetic Admissions...	1,160	Average per year...	232

2.1% All Admissions Diabetic

tions merely because the patient has diabetes mellitus. As long ago as 1890 Lord Moynihan said, "no one should be allowed to die of one disease because he has another." This has occurred in too many instances in the history of diabetes. It is to be emphasized that we may do all types of surgery on the diabetic. This includes emergency operations, elective surgery and even reconstructive and plastic surgery. The important point, however, is to have the patient under adequate diabetic control. This requires the careful coöperation of the internist and the surgeon. The patient should be handled jointly and where possible a combined medical and surgical type of service is the ideal. In too many institutions the interest of the internist or medical resident ceases when the patient is transferred to the surgical service and the reverse also is true. One of the foremost advances in handling problems of this type is the combined clinics and services in which the patient is followed from the time he is admitted by both the medical men and the surgeon. Such a clinic by its proximity and intimate exchange of interests soon develops internists with surgical viewpoints and surgeons who know there is more to diabetic management than the Benedict or Fehling test. One can hope for the establishment of more combined services in our hospitals.

TABLE III—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service

Diabetes and Surgery

Added danger due to:

1. Metabolic inbalance
   - Vomiting
   - Diarrhea and hyperstalsis
   - Starvation
   - Dehydration
   - Acidosis
2. Infection
   - More organism reproduction
   - Less insulin effect
   - Acidosis confuses symptoms
3. Liver function failure
   - Present in diabetes
   - Present in surgical conditions
4. Vacular diseases

Operations on diabetic patients are potentially more dangerous because of certain fundamental weaknesses which patients with diabetes develop (Table III). To control the diabetic there must be a *metabolic balance*. After most abdominal operations there is usually a metabolic upset caused by several factors, one of which is *vomiting*. This may confuse the glucose-insulin regime both by a loss of food intake and by the development of acidosis. The vomitus should be inspected and estimated for food loss and this should be adequately replaced intravenously. Tests for acidosis must be run and this imbalance overcome. The starvation so often present prior to operations or in patients with such a debilitating disease as cancer may deplete the glycogen reserve. In these instances a febrile reaction may reduce the carbohydrate base to a dangerous level. A protein reserve must also be established prior to operation. Diarrhea and hyperperistalsis or the necessity of colostomy or ileostomy results in fluid loss and makes the diabetic control a more difficult problem.

Salt and water balance must be maintained. These are all potentially

dangerous metabolic problems which must be kept more in mind in operating on a diabetic. It illustrates again the necessity for continued medical management by the internist. If the diabetic receives 150 to 200 grams of sugar by mouth or vein in the twenty-four hours after operation with sufficient insulin to utilize it, the danger of acidosis will be slight.

Another source of potential danger to the diabetic is the *post-operative* infection (Table III). There is no evidence that infection develops more often in the diabetic but if an infection does develop, its progress and the loss of diabetic control are more rapid. In the presence of infection insulin is frequently ineffective and in the patient who runs sugar, organisms multiply more readily. This is adequately shown by a high death rate in ruptured appendix in the diabetic. Infection may rapidly direct a patient into acidosis and infection acidosis and acidosis may be difficult to differentiate immediately, as their symptoms are similar. Acidosis with malaise, general abdominal tenderness, pain and vomiting appears like any acute abdominal lesion and may mask an infection for some time. Prophylactic chemotherapy in the major procedures is valuable, particularly in bowel resections. The ability of certain drugs to reduce the bacterial flora in the body should be utilized particularly in these patients. Sulfasuxidine will so greatly reduce the colon bacilli in the colon that it should be part of a routine preparation for operations in this area. Better drugs are becoming available in the near future, and these will reduce further the infection incidence. The necessity for early recognition of a postoperative infection is greatest in the diabetic and diabetic control can be reobtained only when the infection is drained. In addition, operations on the diabetic require a more careful technique–large crushing clamps, heavy ligations and mass ties will be reflected in greater morbidity. Meticulous asepsis and hemostasis is more necessary in this group. "A minor technical error of little moment in the average patient may make the difference between success or failure." An example is the soiling of the peritoneum or wound edge by an appendix stump prior to its cauterization or inversion.

Nearly all diabetics develop liver changes which interfere with glycogen storage and biliary secretion and function. This is true particularly in the severe diabetics and may be sufficient to prevent good control. Many general surgical conditions also lead to liver dysfunction,

the biliary system being a particular offender. A diabetic liver will *not* stand biliary infection and stasis as well as a normal liver. Liver abscesses create a serious problem. Thus an acute cholecystitis will require rigorous diabetic management and early removal.

There are certain diseases to which the diabetic is particularly susceptible. Gall bladder disease has already been mentioned. Autopsies show that one-half of those dying of diabetes have gall bladder disease. These patients should be operated early, prior to the complication stage which will inevitably arise. One cannot expect surgery, no matter how expertly performed, to aid the patient whose liver has been destroyed. There are many doctors whose diabetic patients have diseased gall bladders who believe they are treating their patients correctly by delaying inevitable operations. We feel this is a disservice to the patients as the operation when eventually performed may be at a time when complications make a cure impossible. The risk increases and the ability to surgically cure decreases with the length of time the disease is present. Jaundice in the diabetic greatly increases the operative mortality, possibly due to preventing fat from entering the liver and allowing glycogen deposits. Disease of the pancreas is another condition which patients with diabetes often develop. An acute pancreatitis has been found to be present in one-fifth of all the patients dying in a diabetic coma. This again ties in with biliary tract diseases. Successful handling of such patients requires early operations, i. e., as soon as the diagnosis is made and diabetes controlled.

Goiter is a disease which is incompatible with diabetes. The hyperthyroidism with its rapid metabolism prevents control of the glycemia. Hyperthyroidism interferes with the storage of glycogen or increases its release by an adrenalin-like effect and it is antagonistic to the insulin action. Removal of a diseased thyroid will permit immediate and better diabetic management thereafter. The simple infections as well as boils and carbuncles in the diabetic have been emphasized sufficiently in the literature. Only by repetition, however, do we seem to acquire knowledge. The figure of 20 to 60 per cent mortality from carbuncle in the diabetic has been greatly reduced with chemotherapy, particularly penicillin. There are exceptions, however. One of my patients has had a carbuncle on his face approximately one a year for several years. He develops a leukopenia under sulfa drugs, the first time dropping to 900 leukocytes before the condition was understood. He is also

sensitive to penicillin and each time he appears with this infection of the face the gravity of diabetes and carbuncle is reimpressed on me. The treatment of this infection resolves itself into active and aggressive diabetic therapy and even greater surgical restraint. Chemotherapy must be used and the local wet dressing, if not traumatizing, may help in localizing the lesion and relieving the pain. One can hardly improve on Joslin's edict for the diabetic carbuncle or boil, "Do not squeeze, do not pinch, do not cut and do not run sugar." When there is fluctuation, of course, drainage shortens the course. In respect to these infections I would emphasize again my experience in the value of repeated small blood transfusions. The rationale of such therapy must be understood. It is not to replace hemoglobin and red blood cells but to supply some defensive factor in the circulatory medium in which the patient is deficient. This blood is destroyed by its host in a short time and this defensive factor needs replenishing in two or three days. Not only in the diabetic patient but in innumerable instances of severe infections during the recent war I have seen this factor be the determining one, even in the presence of adequate chemotherapy. The strengthening of the patient's defenses should not be neglected. The benefit of x-ray therapy in localizing these infections early should be remembered and utilized in selected instances. Prophylactically, Brigham emphasized the value of hygiene with, "the washed neck like the watched pot never boils."

The diabetic is as susceptible to the acute abdominal conditions such as appendicitis, or diverticulitis as any other patient. The diagnosis in these instances may be difficult as acidosis may confuse the symptoms or delay the diagnosis. Frequently, the symptoms are insidious and many rupture early. While acidosis causes general abdominal pain and tenderness, a localized tenderness should make one suspect a surgical condition especially if it persists for a few hours despite diabetic treatment. It is well to remember that in a ruptured appendix the diabetes may never be controlled until the peritonitis is drained. In case of doubt operation always should be performed.

Carcinoma.—More operations for cancer are performed today on the diabetic than ever before. The diabetic also is more susceptible to certain carcinomas than other patients. Carcinoma of the pancreas has been found in one-third of the patients who died of diabetes (McKittrick) and one-half of those in Conlin's series.

When the diabetic comes to operation his general medical status should be determined. If the patient is elderly and shows the degenerative arteriosclerosis or cardiovascular change inherent in his disease, the risk will be greater. If not and with diabetic control and management throughout the illness, the mortality should be approximately equal to that of non-diabetics of the same age and in equal status of their cardio-renal vascular systems. We believe it is better if the patient is allowed to run a little sugar. The margin of safety is greater and one is able to tell more readily, the patient's status if shock or coma occurs.

Choice of the Anesthesia.—Local anesthesia is extremely valuable in operations on the abdomen or head but its shortcomings should be understood. Local anesthesia causes increased skin tension and trauma. For this reason it is contraindicated absolutely in operations on the extremities. Some prepared solutions contain adrenalin. Adrenalin is a vasoconstrictor and sugar liberator and should never be used in the diabetic. The various local solutions such as ethyl chloride are likewise contraindicated. Of the inhalation anesthesias cyclopropane is most effective. Ether or chloroform should be avoided. Nitrous oxide with its anoxemia may cause difficulties, especially in a heavily pre-medicated individual. Spinal anesthesia, except in the older age group, is probably the anesthesia of choice for the abdomen. The hypotension accompanying the anesthesia must be prevented if there is marked sclerosis of the peripheral or coronary arteries. Refrigeration anesthesia for operating on the extremities is ideal and will be discussed under amputations. The patient stands a rapid operation more readily than a long one. Glucose and insulin to utilize it should be used during the operation. Postoperatively, the patient should have urine and blood sugars and CO_2 combining power run as often as the severity of the diabetes requires. The patients are particularly susceptible to acid base imbalance and their hydration must be maintained. The value of surgical care combined with medical management is reflected in the mortality figures of less than 4 per cent in over 1,000 major operations at the Mayo Clinic. Early ambulation will reduce the complications and should be utilized. In this early ambulation, non- absorbable sutures are needed. In our hands buried steel wire in the fascia best fulfills the requirements that the suture be strong, easily inserted and with minimal tissue reactions. The reduction of postoperative chest, abdominal and thrombosis complications by early rising we have emphasized before.

Peripheral Obliterative Arterial Disease.—It has been shown quite definitely that arterial sclerotic changes occur many years earlier than we previously thought. In an exhaustive study of all patients without symptoms who were working at forty years of age and over, Wright, Lake and myself reported an incidence of arterial sclerosis in 40 per cent as shown by x-ray and abnormal oscillometric readings. This was much higher than anticipated, but is in line with our present day feelings that sclerotic changes begin ten to fifteen years prior to the development of symptoms. In the diabetic this occurs earlier, especially in the femoral arteries. It is evident that the sclerosis begins as atheromatous changes but involves the walls, too. Joslin's statement that of all diabetics over 40, one-half have femoral sclerosis and that all age groups develop it within five years after the diabetes is discovered may be modified slightly. Certainly, prior to the third decade its appearance can be delayed. Still, approximately one-half of all diabetics die of an arteriosclerotic complication. This group, then, are surgically the most dangerous. With the peripheral sclerosis we have two factors, occlusion and infection. While infection is absent or minimal we treat areas of necrosis and gangrene conservatively, the same as we treat the non-diabetic patient. Toes or sloughs are permitted to self-demarcate, the edges to epithelialize and the dead part to amputate itself. At times, non-traumatizing removal of a dead toe with a rongeur hastens the healing. Any part of the foot that can be retained is saved. No toe or foot amputation requiring anesthesia is performed in this stage. Undermining or pus collections are prevented by sterile soaks and conservative painless debridement of sloughs or saucerizing. To these measures are added three factors, all of which will require careful training of the patient, and it is a duty of the doctor to establish this training, as emphasized by Duryee. These factors are (1) the elimination of all smoking. The part that nicotine plays in patients with arterial occlusion is well established. The occlusion of small collaterals by spasm due to nicotine has been definitely proven. The fact that nicotine itself may be a cause of occlusion other than by spasms is not unlikely. The work of Wright and Duryee, Short, Johnson, Silbert and more recently Weinroth and Herzstein has emphasized this view and there is enough evidence to conclude that if the tendency to sclerose is inherent or acquired, nicotine may precipitate it. In addition, Lundberg and Lundberg have shown a rise in blood sugar of 50 per cent and higher by smoking two

cigarettes, apparently on an adrenalin stimulating basis. We who study and work on the blood vessel system and observe the great part that smoking plays, view with considerable apprehension the nicotine problem. With figures showing that up to 50 per cent of the population will die of cardiovascular renal disease and the certain knowledge that smoking speeds the rate of the disease, it seems time to consider whether the tobacco habit may not be a national scourge.

Youngsters are encouraged to acquire the habit from an early age. National advertising and radio broadcasts constantly extolling the virtues of cigarettes play their part. During the recent war free smokes and smokers made a cigarette a part of each man. Seriously wounded men were given a cigarette even before a dressing or plasma. While in half of the population this may not be too harmful, in the rest a habit of smoking will be definitely deleterious and perhaps one day the deciding factor in the loss of a limb or life itself. In everyone over fifty there is some degeneration present in the arterial tree and this is especially so in the diabetic. The great difficulty of breaking any habit is human and this is particularly true of the smoking one. We believe a campaign on hygienic and preventive medicine lines should have at least equal radio time with such a destructive factor as tobacco. Perhaps we are too vehement but when one has heard strong-minded men admit they cannot give up smoking even to save their limbs the tobacco habit becomes a true physical menace.

The second factor is the prevention of skin breaks and infection This is of extreme and fundamental importance. It requires attention to a hygienic regime in which the feet are cleansed as often and as carefully as the face. Pressure points such as blisters, corns and calluses, and ingrown toe nails must be eliminated by correctly fitting stockings and shoes. Fungus infection, a frequent forerunner for the skin break necessary for secondary infections to enter, must be controlled. In this connection all caustic materials are dangerous. This includes the corn cures and the salicylic and benzoic acid compounds. A very simple preparation of potassium permanganate in from 1:5000 to 15,000 is safe and effective when used for twenty minutes every three to five days. The use of skilled and correct podiatry is important both in the clinic and home and instruction on nail care at home should be given. The third point is an effort to stimulate collateral circulation and reduce spasm in the blood vessels still functioning in the limb. One simple, adequate

TABLE IV—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service

Diabetes Mellitus

Amputation Incidence—1940-1945

	Total 22
Incidence amputation per clinic visit	.0011
Incidence amputation per hospital admission	.018

measure is rest, another is the use of Sitz baths regularly. Postural changes of the Burger exercise type may aid and the Saunder's oscillating bed is another helpful method. Pancreatic tissue extracts have a place in this therapy by their adrenalin-neutralizing effect. It is a little too early to state the part the anti-coagulants, heparin and dicumarol, may play in this respect but we are greatly encouraged by our work on some so far and they may be a decided addition to our therapeutic armamentarium. In a selected group in which spasm is particularly a factor, sympathetic nerve blocks and sympathectomy will prevent or delay the onset of gangrene. This is effected by increasing the capillary blood flows. While there may be some question as to the effect of sympathectomy on the blood supply of muscles, there is no question but what the skin circulation in selected patients is improved and it is in the skin that the gangrene first develops. If sympathectomy is to be helpful it must be performed before gangrene is present. We believe the poor statistical results previously reported from sympathectomy in arterial obliteration were due to the fact that the operation was performed on late cases where gangrene was present; hopeless problems already. Sympathectomy cannot replace dead tissue. If one reserves sympathectomy for those patients with peripheral arterial symptoms when blocks show adequate skin temperature rises, the procedure will be helpful. Sympathectomy was performed in twenty-four patients this last year with only one amputation thereafter necessary and this patient should not have had the sympathectomy performed. It is important that the patient has demonstrated his ability to give up smoking before considering the operation. Whiskey, papaverine and aspirin are vasodilating drugs of some aid. That this conservative type of therapy will be effective in most instances is shown by the amputation incidence at Post-

Graduate Hospital (Table IV); of twenty-two in 18,500 visits of diabetics to the clinic (.0011 per cent) and twenty-two in 1,160 admissions of diabetics to the hospital (.018 per cent).

Local infection once present is difficult to eliminate. In addition, occlusion of local vessels may cause tendon or muscle sloughs. Local amputations of toes may then be required. Wire sutures are placed but not tied in this type of amputation. Where several toes are involved we are interested again in the metatarsal amputation with solar flap, again not closed as discussed by McKittrick. Many of these will heal provided no closure is done and we are proximal to the area of slough. Sterile daily soaks aid healing by removing any collections in the wound. Again let me emphasize that any part of the patient's own foot that he can stand on is better than the most perfect prosthesis.

There are published results on below-knee amputations and their value in rehabilitation. We do not do many below-knee amputations. I believe we save part of the foot in many that others would amputate below the knee. Where spreading infection or gangrene dictates an amputation it is safer above the knee due both to distance from the infection and better blood supply. Once the femoral artery divides, the branches are extremely small. When infection is spreading there comes a time when the decision for operation must be immediate. It is wise to prepare the patient and family for such a possible decision so that there will be no delay at that time.

There is a safe period during which the diabetic can stand a major amputation. If this optimal time passes, like the optimal time for goitre surgery after iodine preparation, it cannot be regained.

Pre-operative preparation should include attention to diabetic control, chemotherapy and adequate local cleansing. The gas forming organisms can be eliminated if the chemotherapy and local cleansing are combined. Clostridium welchii and Bacillus perfringens inhabit the colons of elderly individuals. As these patients are bed ridden, these organisms may be rubbed into the skin. To eliminate them we use three individual skin washings prior to operation. The first scrubbing stimulates the sebaceous glands to secrete and the other ones wash off any organisms thus liberated. In one early case of gas bacillus death we were able later to culture the organism from the skin below the amputation site. Penicillin and prophylactic gas gangrene serum should be used.

After considerable experience we now employ refrigeration anes-

TABLE V—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service

Anesthesia used in Diabetic Amputation

Cyclopropane	20
Refrigeration	16
Local	3
Spinal	1

thesia in all our major amputations (Table V). The technique modified from that of Allen and Crossman consists of introduction of the limb into the icebox for one hour, application of a tourniquet and return to the icebox for one and one-half hours. Operation can then be performed without further anesthesia or without pain provided the sciatic nerve is anesthetized locally before division. This should be done in all anesthetics, as sectioning of the sciatic nerve can cause shock. In one instance the blood pressure dropped to o when the sciatic was divided under nitrous oxide without previous novocaine infiltration. In some, out of diabetic control, the tourniquet performs the functions of amputation; the temperature drops, with no further absorption and diabetic control may be obtained. In these, amputation may be postponed many hours to a safer period. The amputation technique consists of a circular incision at the level of the patella with division of the muscles one inch above the skin edge where they are mostly tendinous and division of the femur directly above the condyles. No muscle or fascial flaps are made and the stump is closed by three or four steel wire sutures through the skin only. No drain is necessary as there is adequate drainage opening between the sutures. The periosteum is not removed from the femur as this periosteal excision may cause a bone necrosis. In some, sulfa powder is applied locally. The wound is dressed and immediate traction applied by weights on a stockinette. The nerve end is treated by simple ligation and severence with a sharp scalpel one-half inch distal to the suture. Phantom limb pain has been no more common with this simple method than after alcohol injections or plastic operations on the nerve. In our experience phantom limb is best treated by forgetting it. Phantom limb is natural after amputation but phantom limb pain is abnormal. Phantom

limb pain is a contagious lesion and one often can prevent its appearance by not suggesting it. On one Navy hospital ship load from Saipan every one of twelve amputees had phantom limb pain. When we questioned the amputees, we found that one of them had a brother who had had phantom limb pain and had told his brother about it. I recall no other phantom limb pain that early in all of the Marine and Navy casualties I saw. Postoperatively the diabetes is watched carefully.

The patient should be out of bed immediately after the operation to reduce complications. We place them in a chair the same day. We cover the stump with oil silk to prevent contamination. The splint permits early movement. Even when weights are applied the patient may be in a chair. The wound is not dressed, unless fever requires it, for ten days. We have had 88.8 per cent primary unions by this technique in contrast to 20 per cent previously. The pre-operative diet and insulin are started at once and if not tolerated, replaced by intravenous feedings. Again, the patient is permitted to run a small amount of sugar until he is stabilized.

One of the most important parts of our service to the diabetic amputee now begins. With the coöperation of the physiotherapy, internal medicine and social service departments we begin rehabilitation at once. The patient is taught to use crutches and to go to the bathroom immediately. Even elderly individuals will learn to use crutches provided they are started early in walkers. Where amputation has appeared inevitable, arm and shoulder exercises have been developed before operations. The patient begins to look forward eagerly to the physiotherapist's visit and we are able with very few exceptions to have these patients walking on crutches when they leave the hospital. This makes them independent and gives them an ambition for an artificial limb. In my experience the diabetic who is relegated to a bed or wheelchair soon dies. I cannot over-emphasize the change this rehabilitation program has made in our amputees. The Social Service contacts the employers and friends and where possible resumption of work, even at home, is started, frequently with the use of other amputees to show the progress that can be made. We encourage the early application of an artificial limb.

Until such time as we are able to control the various factors that cause arterial degeneration, this problem of amputation will be with us. No gadget or mechanical marvel apparatus will be the answer. Careful

TABLE VI—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service

100 *Major Amputations for Vascular Disease*

Diabetes	40	Deaths	4
Arteriosclerosis	38	Deaths	2
Thrombo-angiitis obliterans	4	Deaths	0
Embolic	6	Deaths	4

TABLE VII—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service
Deaths After Amputation for Diabetic Gangrene—1940-1945

	Sex	*Age*	*Time of Death*	*Cause*
1.	Male	72	6 weeks after operation	Cerebral thrombosis
2.	Male	74	Survived guillotine amputation Died 4 weeks after revision	Shock
3.	Female	57	7 weeks after operation	Ascending gangrene of stump into buttocks and abdomen
4.	Female	62	7 days	Infection; refused operation for one month

common sense and conservative measures will help many permanently and the rest until such time as the life of the part is lost and the infection is becoming uncontrollable. Immediate and adequate surgery then will result in the highest percentage of viable patients. The patient who can be taught "to live with his disease and in spite of it with the help of a careful physician will outlive perhaps his undiseased fellow men."

To know one's physical shortcomings makes possible preparation in advance to combat the eventual complication stage. If I may quote again "diabetes is a good disease itself, it just keeps bad company." We must guard against this bad company.

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THE INAUGURATION OF THE

SECTION ON MICROBIOLOGY

GEORGE BAEHR, *President, The New York Academy of Medicine*

THE establishment of a Section on Microbiology represents an important departure from the Academy's tradition. I deem it, therefore, a great privilege to be invited to address the members at this first meeting of the Section. During the first seven years after the founding of the Academy in 1847, its work was carried on through a number of standing committees of Fellows, who concerned themselves with studies and reports upon the burning scientific, clinical and public health questions of the day. The reports of these committees were presented at the Stated Meetings at which, occasionally an essayist from the Academy's Fellowship or a guest from another city would also read a formal paper on some new or controversial subject such as the value of anaesthesia which had been introduced in Boston in 1846 or the revelations of the microscope. In the absence of exact knowlege concerning the cause and nature of infections during those early days, the heated discussions on debatable subjects such as this often aroused prolonged and even bitter controversy among the Fellowship, which were sometimes resumed at a succession of monthly meetings with remarkable tenacity.

By 1854 the growth of the Academy's Fellowship and the failure of some of the committees to function adequately enabled Dr. James Anderson to persuade the Academy to revise its Constitution and By-Laws for the purpose of subdividing the Academy into Sections related to the various clinical and other branches of medicine. Some of the sections were established, therefore, ninety-three years ago. During the past generation standing committees on the library, public health relations, medical education and public medical information have carried on the broader basic responsibilities of the Academy under its charter. But the monthly activities of the eleven, now twelve Sections and of the affiliated societies comprise the actual clinical and scientific life of the Academy.

Until today, all Sections were devoted to clinical medicine, surgery or the various specialties, with the one exception of the Section on Historical and Cultural Medicine. There were several reasons why the officers and council of the Academy were reluctant heretofore to encourage the establishment of Sections dealing with the basic medical sciences. It was feared that they might discourage the presentation of scientific work before the ten clinical Sections which serve as channels for the dissemination of new clinical and scientific information to the physicians of the city and its environs. The officers and council of the Academy also wished to avoid a conflict in interest with the affiliated scientific societies which meet regularly in this building, such as the Society of Experimental Biology and Medicine and the New York Pathological Society.

We are indebted to your chairman Dr. Gregory Shwartzman, and the members of the organizing committee, for convincing the officers and council of the necessity for abandoning our ancient restrictions. I did not need much persuasion for I have long felt that the rapid expansion of our scientific horizons had made it desirable to establish one or more Sections devoted specifically to the basic medical sciences. This is especially true of microbiology which represents a composite field of several overlapping laboratory disciplines but which does not duplicate the essential interests of our affiliated societies. I can foresee the need for at least one other new Section sometime in the future devoted perhaps to the Physical and Chemical Sciences related to Medicine. Its establishment may soon be justified by the phenomenal pace at which these fields of science have grown, especially during and since the War and by their increasing importance for scientific investigation and even for routine clinical diagnosis and therapy. Biophysics, like biochemistry is related to all clinical fields and its technology is expanding so rapidly that it will soon require a place where its experts can assemble and exchange experiences among themselves and among the clinical and scientific workers enrolled in the present Sections of the Academy.

The New York Academy of Medicine is, as you well know, one of the medical cultural centers of this country. Its library is one of the greatest depositories of medical literature in the world. Like its library, the meetings of its various Sections and affiliated societies are open to the medical profession on almost every day in the week. On some eve-

nings as many as five such meetings are held in this building simultaneously. On behalf of the officers and council of the Academy, I take pleasure tonight in welcoming this new venture into our Fellowship. Aside from the many new scientific contributions in microbiology which will be reported at your monthly meetings, I am confident that another of the benefits to the Fellowship of the Academy will come from the effects of your cross-fertilization upon the scientific proceedings of the other eleven Sections and upon the basic work of the Academy in the fields of public health and medical education.

SECTION ON MICROBIOLOGY

NOVEMBER 25, 1947

I. OPENING ADDRESS

ORGANIZATION OF THE SECTION ON MICROBIOLOGY

George Baehr, *President, The New York Academy of Medicine*

II. SCOPE OF SECTION ON MICROBILOGY

Gregory Shwartzman, *Chairman, Section on Microbiology*

III. PAPERS OF THE EVENING

a. Bacteriological aspects of tuberculosis
Rene J. Dubos, Ph.D., Rockefeller Institute for Medical Research

b. Anti-microbial therapy of tuberculosis: The significance of finding of tubercle bacilli resistant to streptomycin in vitro
Walsh McDermott, New York Hospital

c. Modifications of tuberculous lesions in patients treated with streptomycin
John G. Kidd, Cornell University Medical College

IV. DISCUSSION

To be opened by J. Burns Amberson, Bellevue Hospital

Gregory Shwartzman
Chairman
The Mount Sinai Hospital

Harry Most
Secretary
New York University
College of Medicine

Scope of Section on Microbiology

GREGORY SHWARTZMAN, *Chairman, Section on Microbiology*

I would like to begin the outline of the scope by stating that all members of the organizing group, namely, Drs. R. J. Dubos, F. L. Horsfall, Jr., J. G. Kidd, C. M. McLeod, H. Most, R. S. Muckenfuss and myself participated jointly and equally in the organization of the Section on Microbiology.

The task has been indeed a pleasant one due to the interest, encouragement and aid rendered to us by the Officers and the Council of the Academy. In particular, Drs. George Baehr, Waldo B. Farnum, Howard Reid Craig and Mahlon Ashford devoted much time to guide our initial steps.

Our sponsors who petitioned the Council to form this Section have been most generous in their support. The sponsorship by outstanding representatives of various fields of laboratory and clinical sciences affords the opportunity of organizing our work along broad lines dictated by the present-day needs, as we see them.

At the present stage of scientific development, we are confronted with two trends, seemingly opposing each other. Rapid progress necessitates specialization and concentrated efforts in limited fields. On the other hand, there is a continuous widening of the scope and ever-growing alliance of microbiology with other sciences, for mutual benefits.

For instance, some twenty-five years ago investigators dared not compare bacterial chemistry with that of animal cells. It would have been heresy to assume a similarity between the substances supporting bacterial growth and vitamins supporting growth of animal cells. Now we realize how closely related are the problems of bacterial and animal cell nutrition. As a matter of fact, appreciation of this relationship has been greatly responsible for some recent discoveries of vitamins of considerable importance in human nutrition.

Problems of general biology as important as those concerned with the nature of life have confronted the microbiologist investigating the nature of viruses.

The geneticist has enriched microbiology with ideas of genetic dissociation and, by the same token, supplied this science, as well as biochemistry, with new tools for the studies of cellular metabolism. In exchange, immunochemical investigations on type specificity of certain bacteria have unexpectedly assumed significance in genetics since they may aid in the identification of chemical agents involved in hereditary transmission of cellular characteristics.

The botanist and mycologist had long stood in isolation in their preoccupation with the classification of thousands of species of molds. However, the thankless and heroic task of classification has become most valuable when some seemingly useless molds proved to be great human benefactors.

Discoveries of chemotherapeutic agents made by the chemist played havoc with accepted ideas of immunology concerned with specific serum therapy and prophylaxis of certain diseases; while discoveries of antibacterial agents originating from bacteria and molds made by the microbiologist have challenged the skill of the organic chemist in chemical synthesis.

One could go on with examples of this sort, all serving to emphasize that it is most essential for the investigators in biological and medical sciences to be aware of each others problems, and above all, to look for correlation of rapidly accumulating new observations.

Due to its broad interests, The New York Academy of Medicine is best suited to provide a forum for exchange of information between allied groups of investigators. The scope of the new Section must be clearly defined but sufficiently broad in order to serve both the microbiologist and the scientists in allied fields.

The fields of interest to the Section will be bacteriology, mycology and parasitology; viruses and rickettsiae; maladies of unknown and uncertain etiology, possibly of infectious origin; immunology; chemother-

apy; pathology relative to microbiology; and methods of study adopted from related sciences, as applied to microbiology.

Our meetings will be preferably devoted to various aspects of single topics in the form of evening sessions and, from time to time, in the form of more extensive symposia.

Fellows of the Academy interested in the work of the new Section are cordially invited to enroll as its members. The meetings will be open, however, to all interested.

Tonight's session will deal with bacteriological, chemotherapeutic, and pathological aspects of tuberculosis.

We are happy to have Dr. Rene J. Dubos, one of the most outstanding microbiologists, to present the first paper of the first session, the paper on bacteriological aspects of tuberculosis.

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*Bacteriological Aspects of Tuberculosis**

RENE J. DUBOS, PH.D.

The Rockefeller Institute for Medical Research

In contrast to other living cells tubercle bacilli are not readily wetted by aqueous solutions in the usual bacteriological media. As their surface is strongly hydrophobic and lipophilic, the bacilli tend to grow in the form of clumps or pellicles instead of being dispersed throughout the aqueous phase. In addition to being the source of technical difficulties, this mode of growth gives rise to cultures consisting of heterogeneous cell populations. It has been found that a certain wetting agent (a water soluble ester of long-chain fatty acid, known under the name of Tween) has the property of wetting the surface of the bacillus and of permitting dispersed homogeneous growth. The use of this substance in culture media has led to the following findings:

Long chain fatty acids constitute a favorable source of carbon and energy for the growth of tubercle bacilli; other tissue substances (as yet unidentified) can also greatly stimulate the rate of growth. Serum albumin protects the bacilli from the toxic action of many substances which often contaminate bacteriological media. These observations may lead to the development of more rapid and effective techniques for the bacteriological diagnosis of tuberculosis.

The susceptibility of tubercle bacilli to certain antibacterial agents—to penicillin for example—is much increased when the wetting substance, Tween, is added to the test medium. This suggests that the resistance of these organisms may be due in part to the fact that the usual chemotherapeutic agents cannot normally reach the susceptible cellular structure of the bacterium.

Dispersed cultures are very convenient for the production of experimental infections. Inoculation of mice with cultures growing in the dispersed state has led to the following observations:

Mice of different genetic backgrounds exhibit great differences in susceptibility to tuberculous infection.

For any given mouse strain, the rate of development and outcome of the disease is markedly affected by environmental factors; in particular, by the state of nutrition and by other concomitant pulmonary infections caused by filtrable viruses.

The virulence of different cultures of tubercle bacilli for mice (and for other animals) is correlated with marked differences in the morphological and immunological characteristics of the bacilli. It is hoped that the chemical identification of the factors responsible for these differences may lead to a better understanding of the nature of virulence and to a more rational approach to the problem of immunization.

* A complete paper will appear in this *Bulletin* at a later date.

The Significance of the Finding of Tubercle Bacilli Resistant to Streptomycin in Vitro in the Anti-Microbial Therapy of Tuberculosis

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In tuberculosis, as in other infections, when the administration of streptomycin is continued for a sufficient period, to patients with untreated lesions which continue to discharge bacteria, cultures of the obtainable bacteria will grow abundantly in vitro in the presence of high concentrations of the drug. This phenomenon is designated "the emergence" or "the appearance" of "bacterial resistance," and the term "streptomycin-resistant" is used to designate cultures of tubercle bacilli which grow readily in vitro despite the presence of 100 micrograms of streptomycin per cc. of medium. It should be noted that the data to be presented should not be applied to meningeal tuberculosis which is treated with high concentrations of streptomycin administered by the intrathecal route.

The speed with which bacterial resistance appears varies considerably, depending upon the species of the infecting microorganisms. In the series of approximately 100 tuberculous patients which Dr. Muschenheim and I have been studying for the past two years, the earliest detection of drug-resistant cultures was after five weeks of streptomycin therapy. In general, however, the initial appearance of the phenomenon was detected between the sixtieth and the ninetieth day of treatment.

If drug-resistance demonstrable in vitro reflects the presence of a drug-resistant infection, it follows that the total period during which streptomycin might be of value would usually be limited to only one to three months. There has been some reluctance to accept the notion that tubercle bacilli which are drug-resistant in vitro, are similarly drug-resistant in the patient.

One observation which leads some to skepticism is the fact that in certain patients the first conspicuous roentgenologic improvement has been observed during the third and fourth months of streptomycin therapy at a time when the cultures obtained from the patient are streptomycin-resistant.

Another reason for questioning the significance of the finding of drug-resistant cultures is the fear that the conditions of in vitro testing could be such that a culture containing only a small percentage of drug-resistant cells would falsely appear predominantly or uniformly resistant.

Obviously, the validity of the latter objection would depend upon the conditions of the in vitro testing. The particular test used in our own studies is a serial dilution method in which the albumin-Tween medium of Dubos and Davis is used.

Examination of the material from the clinical study, in which this test was used, provides evidence for proper consideration of these questions.

The course under continued streptomycin therapy of patients with hematogenous or pulmonary infections who continue to discharge drug-resistant bacilli was presented. On the basis of these observations, it was concluded:

1) The continued administration of streptomycin to patients who continue to discharge tubercle bacilli results in the emergence of bacterial resistance usually within sixty to ninety days of the start of the antimicrobial therapy.

2) In generalized hematogenous tuberculosis, it appears certain, and in pulmonary tuberculosis, highly probable, that the emergence of streptomycin-resistant organisms (under the conditions of the test employed) indicates the presence of an infection which is drug-resistant in the patient.

*Modifications of Tuberculous Lesions in Patients Treated With Streptomycin**

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During the past year seven patients who had been given streptomycin in the treatment of miliary tuberculosis have been examined postmortem in the Department of Pathology of The New York Hospital—Cornell Medical Center. In all of these cases there was evidence that the tuberculous lesions had been modified by the therapy.[1]

In one patient, for example, extensive miliary tuberculosis of the lungs, demonstrated roentgenologically, had resolved completely after about thirty-five days of therapy, while an associated tuberculous meningitis at first had responded to the drug given intrathecally but eventually had relapsed, causing an internal hydrocephalus and death 297 days after the initial diagnosis had been made. Gross examination of the lungs postmortem revealed no trace of miliary lesions, and cultures of the lungs for acid-fast bacteria were negative, though a healed primary complex was found. Microscopically, there were many small scars consisting of loose fibrous tissue scattered irregularly throughout all lobes of the lungs; these revealed no evidence of active tuberculosis, and they were interpreted as being the healed remains of miliary nodules (Figure 1).

In still another patient, miliary tubercles of the lungs had disappeared following the initiation of drug therapy, as indicated by x-ray examinations, and a tuberculous lymphadenitis had subsided notably. The miliary tubercles reappeared, however, and the lymph nodes enlarged again some weeks later in spite of continued chemotherapy, and during this relapse tubercle bacilli isolated from a cervical node proved markedly resistant to the effects of streptomycin, growing in the presence of 1000 units of the drug per cc. of medium, whereas those that had been isolated prior to treatment were inhibited by a concentration of 1.5 units per cc. On postmortem examination very many large miliary tubercles were visible in the lungs; these were discrete, spherical, and about five times the size of the usual hard miliary tubercles; microscopically each tubercle was composed of a thick fibrous capsule arranged concentrically about an area of caseation and granulomatous inflammation that often had broken through the fibrous barrier and more or less surrounded the latter (Figure 2). These lesions contained great numbers of acid-fast rods, as special stains revealed, and their "inside-out" character made it seem that the disease process had been held in check for a time and then gained overwhelming impetus, perhaps when bacterial variants resistant to streptomycin had become prevalent in the lesions.

Focal scars similar to those already described were seen in the lungs of the remaining five patients, all of whom had responded temporarily to the drug therapy, though in four of these cases active tuberculosis was more or less widespread throughout the lungs or in the central nervous system in addition; often healed lesions and active ones were present side by side in the same microscopic field. In every case where the scars of healed miliary tubercles were found in the lungs they were likewise present in other viscera, notably in the liver, spleen, and kidneys. There was also evidence, both clinical and anatomical, of healing of tuberculous meningitis in three of the cases, yet it is noteworthy that the meningeal process was more or less active at the time of death in six of the seven patients. As previously reported,[1] the anatomical findings in general were quite similar to those noted by Baggenstoss, Feldman, and Hinshaw in

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Figure 1. The scar of a healed miliary tubercle in the lung in a case of streptomycin-treated tuberculosis (Case No. 1—12164). Small scars such as this, scattered irregularly throughout all lobes of the lungs, were the sole remains of an extensive miliary tuberculosis in this case. Similar areas of focal fibrosis were found in the lungs in all of the 7 cases here reported.

Figure 2. An "inside-out" tubercle, great numbers of which were present in the lungs of Case No. 3—12092. These modified tubercles are much larger than ordinary hard tubercles and are composed of a partially caseous center surrounded by a thick rind of fibrous tissue through which the active process has extended to form a broad outer layer of tuberculous inflammatory tissue. It is noteworthy that acid-fast bacilli, presumably markedly resistant to streptomycin (see text), were present in great numbers in these lesions, both in the outer inflammatory zones and in the caseating centers.

five cases of miliary tuberculosis that had been similarly treated with streptomycin.[3]

The fact deserves special emphasis that in five of the seven patients the tubercle bacilli isolated some days or weeks after streptomycin therapy had been instituted and during a period of relapse were markedly resistant to the action of streptomycin, often growing uninhibited in the presence of 100 to 500 units of streptomycin per cc. of culture medium, whereas the bacilli that had been isolated prior to treatment in every case had failed to grow in media containing 2 units or less per cc. In four of these cases a close correlation could be made between the clinical remission followed by relapse, the presence in the lungs or in the central nervous system of older healed lesions and newer active ones, and the manifestation of drug-fastness by the bacilli isolated in the terminal stages of the disease.

From a consideration of the findings as a whole, it seems plain that streptomycin therapy may greatly modify the character of the lesions in miliary tuberculosis, and the inference seems warranted that the disease process may often be largely overcome by the combined influences of the drug and the body's defences, only to "light up" later when drug-fast microorganisms become dominant in the lesions. In addition, the postmortem studies have disclosed the pathogenesis of another limitation in the use of this drug. For five of the patients in the group had become partially deaf as a result of its toxic action, and several exhibited marked vestibular dysfunction as well; all of these patients showed degenerative changes in the neurones of the 8th cranial nerve nuclei, the cellular abnormalities ranging from an hydropic degeneration of cytoplasm to complete liquefaction necrosis, while similar changes were found in the ventral cochlear nuclei of three dogs given massive doses of streptomycin experimentally.[3]

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It is of course gratifying to the pathologist to be able to bring anatomical findings such as these into close apposition on the one hand with the natural history of a disease process, as portrayed here by the

precise observations of my clinical colleagues, and on the other hand with etiological factors, as exemplified in these cases by the detailed studies of the infecting microorganism made in the laboratory of my distinguished predecessor on this evening's program; for such is one of the main functions of the pathologist. But the essential facts of these studies may be viewed with pleasure also in a much larger frame of reference. For nowadays the anatomy of infectious disease processes is notably different to what it was only a few years ago, thanks to the widespread use of the sulfonamides, penicillin, and the newer antimicrobic agents. For example, Hugh Cairns and Dorothy Russell have recently described proliferative and necrotizing cerebral arteritis and phlebitis in cases of pneumococcal meningitis that survived 7 weeks or longer under treatment with penicillin, the lesions having not been seen in prechemotherapeutic days when death from this disease invariably occurred within a week or two.[4] And everyone who reviews large numbers of postmortem examinations has, I am certain, been impressed with the relative paucity of the infectious lesions that now pass under his eye. To cite in general terms a part of our own experience in this relation I may say that we have not had a case of pneumococcal lobar pneumonia on the necropsy service of The New York Hospital—Cornell Medical Center during the past four years and the number of clinically-significant bronchopneumonias due to pneumococci, streptococci, and staphylococci has sharply diminished, while those now appearing are often milder, with more resolution and less inflammation than used to be seen in such cases. If the effectiveness of our armamentarium against infectious diseases continues to increase during the next few years as it has in the past decade—and the new Section on Microbiology of The New York Academy of Medicine is largely dedicated to this end—we may look forward to the day when the pathologist will no longer see infectious disease processes at all, except when he chooses to create and study them in the experimental animal for his further enlightenment. Soon may that day dawn!

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